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THE PROCESS OF DIFFERENTIATION OF THE RETINAL LAYERS IN VERTEBRATES*

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THE development of the various nuclear and fibrillar layers of the adult retina from the undifferentiated neural ectoderm of the walls of the optic cup is a complicated process. Nevertheless a study of its stages in animals representative of the various classes of vertebrates brings out the interesting fact that a basal plan exists for the entire phylum. Modifications, usually in the form of abbreviation or slurring over of stages, occur from time to time, but in all the animals examined the principle of the differentiative process remained unchanged and was exemplified in the most primitive as well as in the most specialised types. Superimposed on this basal arrangement there was also apparent a slow evolutionary increase in efficiency, brought about rather by alteration in size and appearance than by modification of arrangement of the anatomical elements involved.

It is proposed to deduce by examination of various species both the fundamental plan and the mechanism of evolutionary improvement on it.

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The earliest period of development which concerns us is that immediately after the invagination of the primary optic vesicle to form the optic cup. The changes to be described involve principally the inner wall of the cup, which, at its inception, is composed of a neuro-epithelium throughout the entire thickness of which are scattered oval nuclei, no cell boundaries being distinguishable. The outer wall of the optic cup is composed of a thinner neuro-epithelium containing only a single row of nuclei. It remains in this condition throughout the entire life of the individual. The only changes which occur in it beyond increase in area are connected with its pigmentation. The nuclei of the inner wall, on the other hand, must become as it were sorted out and re-arranged in definite layers divided by fibrillar intervals before they can resemble the adult condition. The nuclei themselves must also undergo differentiation, which is always signalised by a change of outline from oval to circular, while in addition the protoplasm of the cell body must become distinct from the original mass.

It may be stated as a general rule that differentiation of nuclei begins in those nearest to the inner surface of the optic cup and spreads gradually outwards. This differentiation is accompanied at first by migration of the nuclei towards the inner surface, so that, soon after the beginning of the process, two nuclear layers can be recognised, an inner composed of round nuclei and an outer composed of oval nuclei. These will be referred to as the *inner* and *outer neuroblastic layers* respectively. From them the layers of the adult retina are developed. Since differentiation spreads from the inner surface of the retina outwards it follows that the conducting and supporting mechanism is developed in advance of the receptor itself. This order is of common occurrence throughout the embryo, in which as a general rule development progresses from less specialised to more specialised organs and tissues.

Cyclostomes

The Cyclostomes represent the lowest known type of vertebrate. They are usually classed with the fish, but differ from them (and indeed from the rest of the vertebrates) in certain important particulars, for example in the absence of a branchial skeleton and in the persistence of the notochord. *Petromyzon fluviatilis* (the lamprey) may be taken as an example. In the larva (known as *Ammocoetes*) the optic cups are present as outgrowths from the forebrain, but are not yet in direct contact with the surface ectoderm. During the third year metamorphosis takes place, the eye reaches the surface and a lens is developed. Long before this,

however, the process of differentiation has begun in the wall of the optic cup and the retinal mechanism is complete before the end of the larval stage.

Fig. 1 shows the beginnings of retinal differentiation. The optic cup is seen lying empty and folded against the side of the fore-brain, embedded in the myotomic muscles. The portion of the cup lying above the insertion of the optic stalk shows commencing

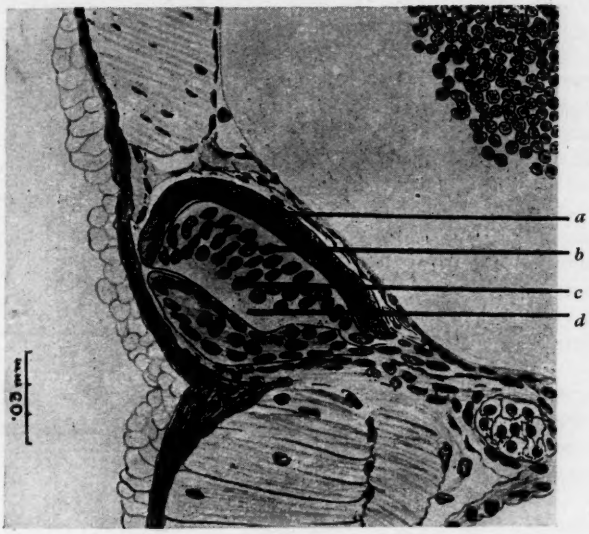


FIG. 1.

Developing eye of Petromyzon fluviatilis. Early stage.

a = pigment layer.
b = outer neuroblastic layer.
c = inner neuroblastic layer.
d = marginal layer.

differentiation. The cells of the outer layer contain pigment granules, while those of the inner layer, which is about three and a half times as thick as the outer, are beginning to show typical changes. This inner layer can be divided into a nucleus-free inner zone and an outer zone containing nuclei of two kinds. The inner zone is known as the marginal layer. It is comparable with the marginal layer which appears throughout the developing central nervous system and reaches its acme in the embryonic spinal cord. (The marginal layer, wherever it occurs, seems to

act as a nidus for the reception of cells formed by division of nuclei in the layers deep to it and of the nerve fibres developed from these cells.) The innermost nuclei of the nuclear zone are circular in outline (*i.e.*, they are already specialised for function rather than

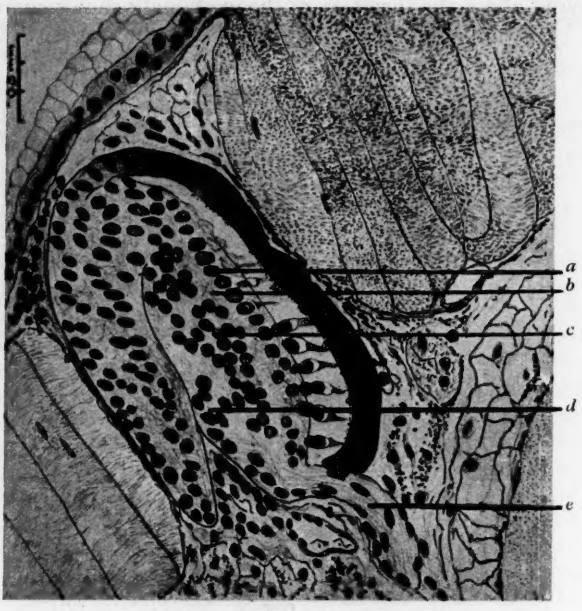


FIG. 2.

Later stage of developing eye of Petromyzon fluviatilis.

a = outer nuclear layer.
b = outer molecular layer.
c = inner nuclear layer.
d = ganglion cells and nerve fibres.
e = optic stalk.

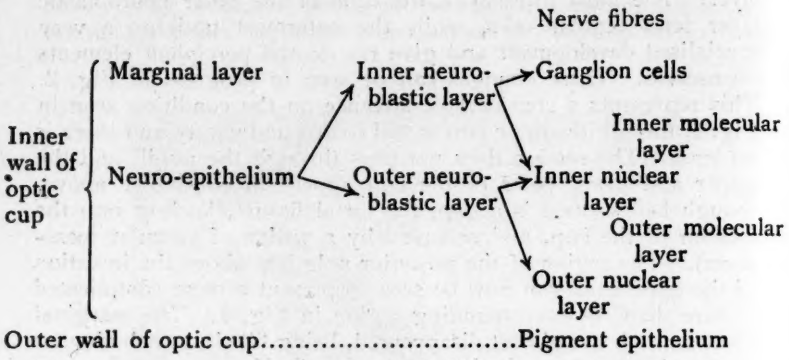
division.) They form a more or less irregular single row encroaching on the marginal layer and constitute the *inner neuroblastic layer*. The two rows of undifferentiated oval nuclei lying outside this constitute the *outer neuroblastic layer*. Those abutting on the pigment layer undergo karyokinesis and by their division add both to the size of the eye and to the number of nuclei internal to themselves. They are the last to differentiate. Before they do so, the inner neuroblastic layer has migrated further into the marginal

layer and its cells have given rise to axons which, running in the marginal layer parallel to the surface, constitute the nerve fibre layer. The most internal of the cells of the outer neuroblastic layer form bipolar cells, while the outermost undergo a very specialised development and give rise to the percipient elements themselves. These changes can be seen in progress in Fig. 2. This represents a considerable advance on the condition seen in Fig. 1, though the optic cup is still folded and empty and there is no lens. (The section does not pass through the pupil, and the upper and lower parts of the cup appear in continuity above, though below there is a gap, the foetal fissure, leading into the interior of the cup, and occupied by a wedge of vascular mesoderm). The region of the posterior pole just above the insertion of the optic stalk can now be seen to present a more complicated picture than the corresponding region in Fig. 1. The marginal layer as such has almost disappeared, being filled up with circular nuclei (derived from the inner neuroblastic layer) and with nerve fibres. The nuclei are those of the ganglion cells. The nerve fibres run downwards and, entering the optic stalk, pass backwards to the brain. They appear, as in all the animals examined, coincidentally with the ganglion cells and in many instances can be seen developing as actual processes of these. Their early advent exemplifies the general rule mentioned above of appearance of conducting layers before percipient.

Deep to the ganglion cells and nerve fibres are two or three rows of irregularly arranged circular nuclei, the most superficial of which appear to lie within the original marginal layer, while the more deeply placed ones correspond in position with the innermost nuclei of the outer neuroblastic layer of the previous stage. These round nuclei constitute the inner nuclear layer and are separated by a narrow interval, the outer molecular layer, from a single row of nuclei connected with the developing percipient elements. These latter are all of one type, very large and separated from each other by wide intervals. Various stages in their formation can be recognised in the figure. (We are not concerned here with details of structure, but only with the mechanism of differentiation of layers, so that the individual elements need not be described further.)

We can, therefore, recognise at this stage the typical layering of the adult retina. Of these the nerve fibre and ganglion cell layers have developed from the *inner* neuroblastic layer of the previous stage, the inner nuclear layer appears to contain elements from both *inner* and *outer* neuroblastic layers (though they cannot be easily distinguished apart) and the outer nuclear layer (or nuclei of the percipient elements) has formed by differentiation of the outermost (proliferating) row of nuclei of the *outer* neuro-

blastic layer. This may be represented simply by a scheme, thus :—



It is to be noted that, although the layering in Fig. 2 is that of the highest vertebrates, it is not possible to distinguish so many elements as in their retinae. Fibres of Müller, amacrine cells and horizontal cells cannot be recognised definitely at this the corresponding stage in Petromyzon to that at which they are evident in higher forms.

Fish

As an example of a primitive fish, the Ganoid, *Amia calva* (American bowfin) has been chosen. The early stages of growth of the optic vesicle and the invagination of it to form the optic cup follow the usual vertebrate lines. Pigmentation begins in the outer layer of the optic cup at a time when the inner layer has still the character of a simple neuro-epithelium with ten to twelve rows of oval nuclei. The differentiation of the pigment layer progresses a stage further than it does in Petromyzon, since the cells develop flame-shaped processes from their inner surfaces, which processes pass up between the outer limbs of the rods when these appear. This condition is common in most of the vertebrates below the mammals.

With regard to the inner layer, we see in Fig. 3 that the first sign of differentiation is (as in Petromyzon) a change of shape of the most internal nuclei from oval to circular. There is not, in fish, at any time a well-marked nucleus-free marginal layer. This, occurring as it does in Petromyzon, and also in other species and in other parts of the central nervous system, may be looked on as a primitive stage which is slurred over or abbreviated in the fish. This abbreviation may be correlated with the relatively short

larval stage of fish as compared with Cyclostomes and is probably merely a means of ensuring rapidity of development. In Fig. 3 we can recognise therefore the commencement of the formation of the inner neuroblastic layer from the innermost cells of the neuro-epithelium. These first cells to differentiate will become ganglion cells and give rise to nerve fibres long before the outermost cells have begun to specialise. In Fig. 3 these outer cells can be seen

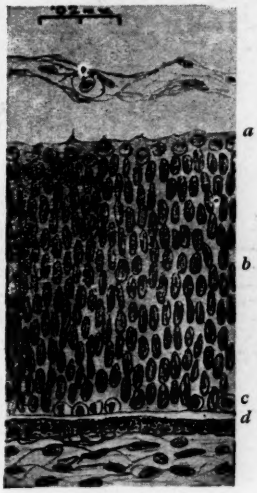


FIG. 3.

Early stage of differentiation of the retina of the Ganoid fish, *Amia calva*.

a = beginning of inner neuroblastic layer.
b = undifferentiated neuro-epithelium.
c = proliferating layer.
d = pigment layer.

undergoing mitosis, and forming a proliferating layer next the basement membrane.

The inner neuroblastic layer increases in thickness by increment of cells external to it. Nerve fibres arise from its innermost cells and form a nerve-fibre layer on its inner surface. Fig. 4 shows an eye in which this is occurring. The layers at the posterior pole here consist of an innermost nerve fibre layer, an inner neuroblastic layer of round nuclei, and an outer neuroblastic layer of oval nuclei, those in the outermost row of all being in a state of active proliferation. After this stage the inner neuroblastic layer increases in thickness and becomes divided into an inner and an

outer band by a fibrillar layer, the inner molecular layer. The cells of the outer band are separated from those of the outer neuroblastic layer by a very narrow interval (the "transient fibre layer" described by Chiewitz* in human embryos), but are as well easily distinguishable from them by containing slightly less chromatin

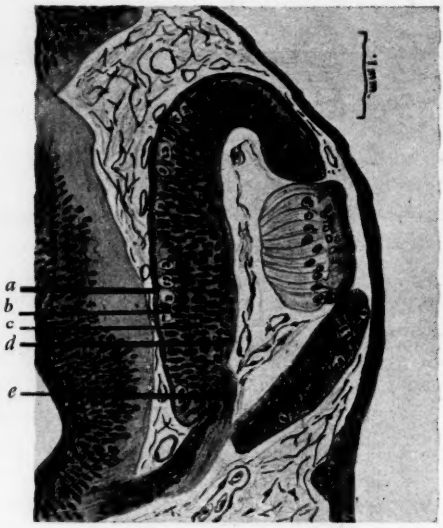


FIG. 4.

Developing eye of *Amia calva*.

a = pigment layer.
b = proliferating layer.
c = outer neuroblastic layer.
d = inner neuroblastic layer.
e = nerve fibre layer.

in the nucleus, and in consequence staining less deeply. Soon after the appearance of the inner molecular layer the specialisation of nuclei begins to involve the outer neuroblastic layer as well. Its nuclei become in turn spherical and separated into two bands, an outer and an inner, by a fibrillar layer, the outer molecular layer. When this has occurred the retina consists of four bands of nuclei, separated from each other by three fibrillar layers, of which the centre one, or transient fibre layer of Chiewitz is very narrow.

*Chiewitz, J. H.—*Intern. Zeitschr. f. Anat. u. Physiol.*, Vol. IV, p. 201, 1887, and *Anat. Anzeig. Jena*, III, 579, 1888.

Fig. 5 shows this stage. The four nuclear layers from within outwards can be recognised as the ganglion cell layer, a layer of spherical nuclei which later form amacrine cells, a layer of more darkly staining bi-polar nuclei, and a layer of nuclei, still oval, in connection with which the percipient elements are just beginning to develop. The transient layer of Chiewitz disappears very

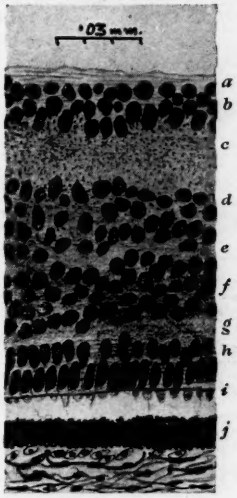


FIG. 5.

Developing retina of *Amia Calva*.

a = nerve fibre layer.
b = ganglion cell layer.
c = inner molecular layer.
d = amacrine cell layer.
e = transient fibre layer.
f = bi-polar layer.
g = outer molecular layer.
h = rod and cone nuclei.
i = developing rods and cones.
j = pigment layer.

soon and the second and third nuclear layers then fuse to form the definitive inner nuclear layer, from the outermost elements of which horizontal cells are formed during the next stage. We thus see that the complexity of the inner nuclear layer foreshadowed in Petromyzon is now clear. It contains three types of cell :—

1. amacrine cells, derived from the inner neuroblastic layer,
2. bi-polar cells, and
3. horizontal cells, which two latter types are derived from the outer neuroblastic layer.

Fig. 6 shows the end result of the disappearance of the transient fibre layer and the formation of the horizontal cells. In this, the retina of an advanced embryonic stage of Amia, one can recognise three bands of cells; the innermost is the ganglion cell layer. The

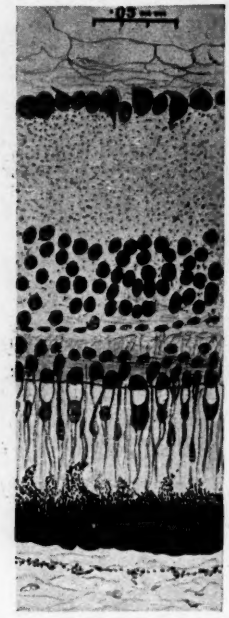


FIG. 6.

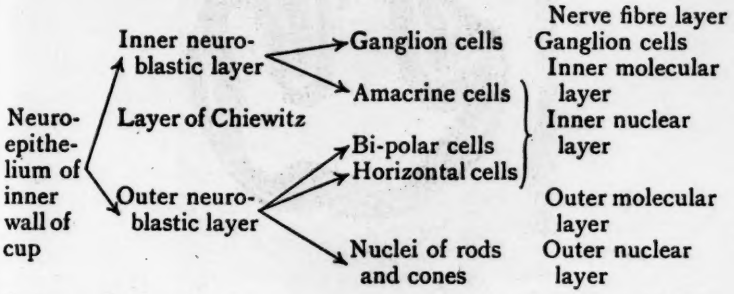
Retina of advanced embryo of *Amia Calva*.

a = nerve fibre layer.
b = ganglion cells.
c = inner molecular layer.
d = amacrine and bi-polar nuclei.
e = horizontal cells.
f = outer molecular layer.
g = rod nuclei.
h = cone nuclei.
i = rods and cones.
j = pigment layer.

outlines of the cell bodies are here visible. Nerve fibres are forming a thin layer internal to them. Deep to the ganglion cell layer is the inner molecular layer. This is relatively very wide, a condition characteristic of vertebrates below the mammals. The next cell layer is the inner nuclear layer. It contains amacrine and bi-polar cell nuclei, now not to be distinguished from each other, and is bounded externally by a single row of horizontal cells. Outside it lies the outer molecular layer and outside this the nuclei of the percipient elements. These latter are clearly of two kinds, rods

and cones. The nuclei of the rods are small and lie internal to the larger cone nuclei. The pigment epithelium shows flame-shaped processes.

The differentiation of the retina of Amia is therefore more complete than that of Petromyzon, though in principle it is similar. It may be reduced to a scheme thus:—



It is to be noted that as yet the retina contains no demonstrable supporting tissue. Fibres of Müller cannot be recognised as such though it is probable that some sort of undifferentiated glial scaffolding does exist. This paucity of recognisable supporting tissue (in stages corresponding to those in which it is clearly recognisable in higher forms) may perhaps be looked on as merely part of the low grade of development of such tissues throughout the body, *e.g.*, the major part of the skeleton in fish never reaches the stage of ossification and the connective tissues generally often show a less degree of condensation than they do in higher animals.

A further example may be cited among fish, namely the Elasmobranch, *Squalus acanthias*, the dogfish. In this animal the same abbreviation of early stages is apparent, and there is moreover greater difficulty in distinguishing the various types of cell than there is in Amia. The main plan of differentiation is similar, but the details are not so clear cut. There is the same paucity of glial scaffolding as in Amia. Fig. 7 shows an early stage of the primary optic vesicle in which the entire wall consists of undifferentiated neuro-epithelium. Fig. 8 shows the eye of an older dogfish. It represents a stage when invagination is complete and the distinction between the thin outer and thick inner layer of the cup is well marked. The inner layer shows a very narrow marginal layer, which soon becomes filled up with nerve fibres arising from the cells immediately subjacent to it. These ganglion cells appear to be relatively late in separating from the underlying

FIG. 7.
Optic vesicle and forebrain of dogfish embryo.

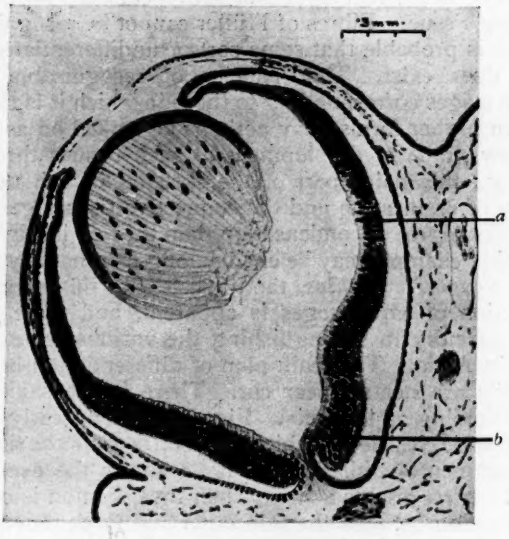


FIG. 8.
Section through optic cup of dogfish embryo.
a = marginal layer.
b = nerve fibres.

layers. Fig. 9 shows a portion of the retina of a young dogfish in what is generally known as the "pup" stage. The nerve fibre layer is thick, but the inner molecular layer is still narrow, and the ganglion cell nuclei are arranged in three rows. There is no distinction between amacrine, bi-polar and horizontal nuclei; together they form an inner nuclear layer of seven rows deep. The rods and

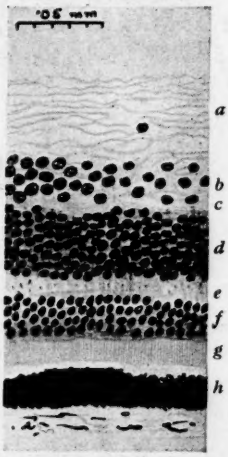


FIG. 9.

Retina of dogfish ("pup" stage).

a = nerve fibre layer.
b = ganglion cells.
c = inner molecular layer.
d = inner nuclear layer.
e = outer molecular layer
f = outer nuclear layer.
g = rods and cones.
h = pigment layer.

cones are present and their nuclei are arranged in four rows. The pigment epithelium is a dense black. Processes from it are not well marked.

The true fish thus shows an advance on the Cyclostome in that a greater variety of cells can be recognised, though the main arrangement is the same in both types.

Amphibians

In the Amphibia the same principles of differentiation appear to hold good, but the process can be followed one stage further, namely, to the formation of a distinct glial system with well-formed Müllerian fibres. The retina of the frog tadpole seen in

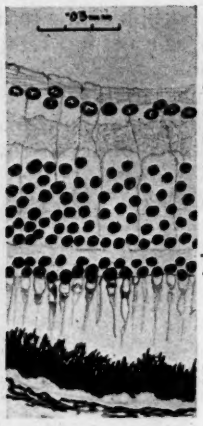


FIG. 10.

Retina of frog tadpole.

a = nerve fibre layer.
b = ganglion cells.
c = inner molecular layer.
d = amacrine cells and fibres of Müller.
e = bi-polar cells.
f = outer molecular layer.
g = outer nuclear layer.
h = rods and cones.
i = pigment epithelium.

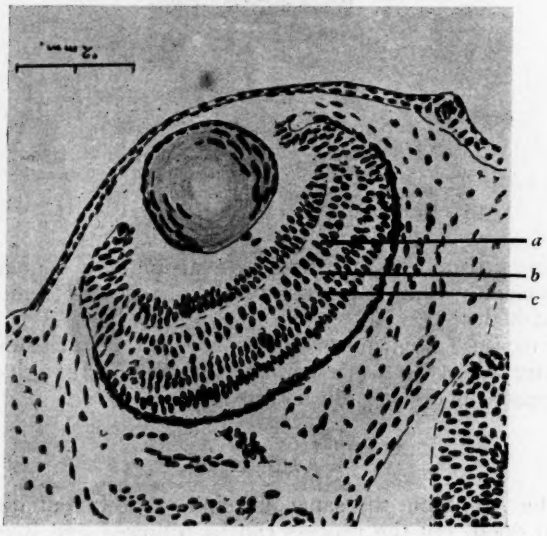


FIG. 11.

Developing eye of Necturus.

a = amacrine cells.
b = layer of Chiewitz.
c = bi-polar cells.

Fig. 10 shows these fibres running from the internal limiting membrane to the outer molecular layer. Their nuclei (which lie in the inner nuclear layer) are not easy to distinguish. Amacrine cells occur on the inner surface of the inner nuclear layer, but horizontal cells are not apparent, a difference from the condition found

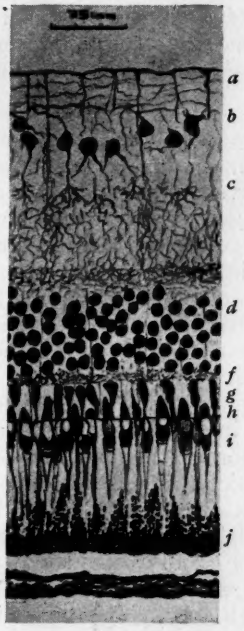


FIG 12.

Retina of frog.

a = nerve fibre layer.
b = ganglion cells.
c = inner molecular layer.
d = amacrine and bi-polar nuclei.
f = outer molecular layer.
g = rod nuclei.
h = cone nuclei.
i = rods and cones.
j = pigment layer.

in Amia. It is not possible in Amphibia to make out for certain the layer from which come the nuclei of the Müllerian fibres. Their appearance at this stage is, however, interesting. It may possibly be correlated with the more generally advanced supporting tissues of these animals. That the amacrine cells in Amphibia as well as in other orders come from the outer neuroblastic layer, and secondarily fuse with the layer of bi-polar nuclei to form the inner nuclear layer can be seen from the stage of Necturus seen in Fig. 11.

Here the amacrine nuclei are arranged in two rows separated from the ganglion cell nuclei by the inner molecular layer and from the bi-polar nuclei by an interval which from its position is the transient fibre layer of Chiewitz. Subsequent fusion of these two nuclear layers (amacrines and bi-polars) produces the definitive inner nuclear layer. Fig. 12 shows the adult condition in the frog. It differs from that of Amia (Fig. 6) in the presence of fibres of Müller and the absence of recognisable horizontal cells. Otherwise the two are exactly similar.

Reptiles

The developing reptilian retina is in some ways more primitive than that of the fish, in that it does not show abbreviation of stages. This leads to a relatively slower rate of differentiation, and hence the successive changes are clear cut and can be more easily followed. Like that of the Cyclostome, Petromyzon, the reptilian retina passes through a stage in which the inner wall of the optic cup consists of a neuro-epithelium having a nucleus free marginal layer on its inner surface, and deep to this a mantle-layer of oval nuclei, the outermost row of which is in active mitosis and forms the proliferating layer. At this stage the appearance of the wall of the cup is very similar to that of the spinal cord, which, in early stages, differentiates in exactly the same way. From the nuclei of the mantle layer are formed the inner and outer neuroblastic layers. The inner neuroblastic layer arises by the migration of the innermost nuclei of the mantle layer into the marginal layer. At the same time these nuclei change their outline from oval to circular. They can be seen in Fig. 13 (which shows the eye of a *Chrysemys marginata* embryo) as a single row (containing only five cells) lying in the marginal layer. This migration continues, and very soon processes develop from the innermost of the migrating cells, which run in the marginal layer at right angles to its surface, and, passing towards the region of insertion of the optic stalk, turn into the inner layer of this to form the nerve fibres of the optic nerve. The first of the retinal cells to differentiate are therefore the ganglion cells (as in all the other species examined). They can be seen in Fig. 14, which also shows their axons running into the optic stalk.

The inner neuroblastic layer thus formed increases in thickness. Its innermost cells form ganglion cells as we have seen, but its deeper cells undergo differentiation in another way. Like the ganglion cells their nuclei become circular, but they do not send axons into the nerve fibre layer. Instead they become separated from the ganglion cells by an interval (the inner molecular layer) and form a more or less distinct row (recognisable as the amacrine layer) separated from the outer neuroblastic layer by a fibrillar

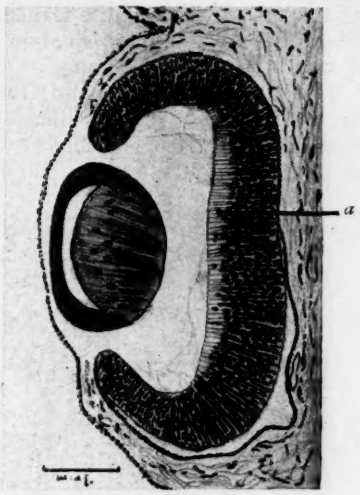


FIG. 13.

Section through the optic cup of a young Chrysemys marginata embryo. *a* = cells of inner neuroblastic layer migrating into marginal layer.

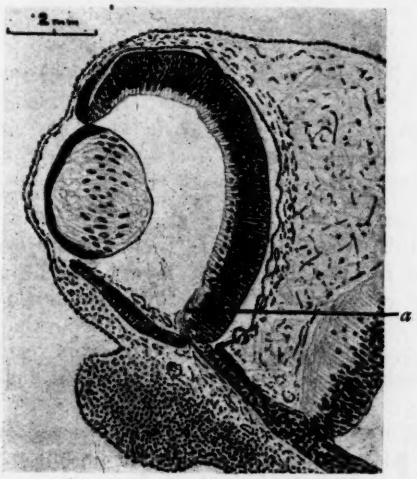


FIG 14.

Slightly older stage of Chrysemys marginata. *a* = nerve fibres appearing in marginal layer.

interval of varying thickness. This is the transient fibre layer of Chiewitz. It can be seen in Fig. 15, which shows a few amacrine cells in process of separation from the ganglion cells. This continues until they form a considerable band, the transient fibre layer diminishing in thickness meanwhile. This disappears finally and they fuse with the outer neuroblastic layer to form the final inner nuclear layer, though they can long be recognised as

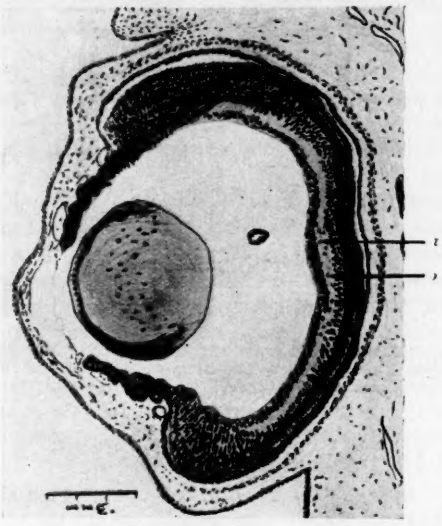


FIG. 15.
Section through the eye of a Chrysemys marginata embryo.
a = amacrine cell, separating from ganglion cell layer internal to it.
b = transient fibre layer.

distinct from this. Fig. 16 shows them forming a layer on the surface of the outer neuroblastic layer, which has meanwhile divided into an inner bi-polar layer and an outer layer of rod and cone nuclei. These are separated from each other by the outer molecular layer, and the definitive condition is reached merely by thinning of nuclear and thickening of fibrillar layers as the eye enlarges.

The reptiles show definite fibres of Müller (Fig. 16). Their nuclei are not easy to see, but appear to lie among the amacrine cells and to be developed with them from the outer neuroblastic layer.

The reptilian retina therefore shows the stages of differentiation very clearly, and they may be reduced to a scheme which will be

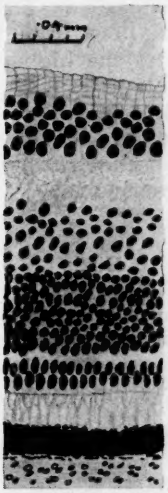
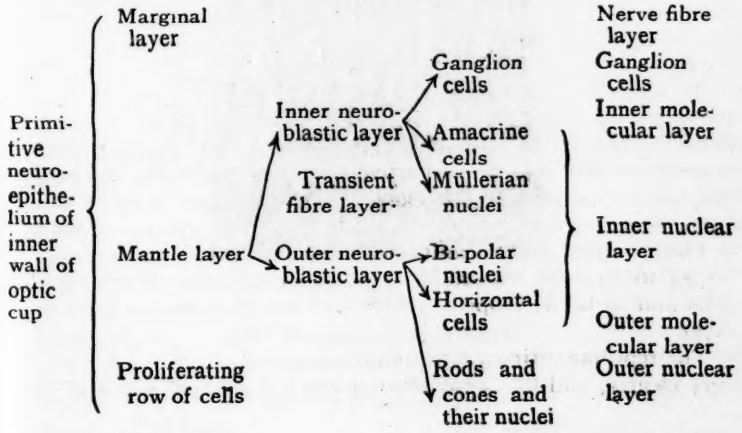


FIG. 16.

Retina of Chrysemys marginata embryo.

a = nerve fibres and Müllerian fibres.
b = ganglion cells.
c = inner molecular layer.
d = amacrine cells.
e = bi-polar cells.
f = outer molecular layer.
g = outer nuclear layer.
h = rods and cones.
i = pigment layer.

found to be appropriate to all the classes above them. It will be seen to resemble very closely the primitive Cyclostome type, merely differing from that in greater elaboration and distinctness of stages.



Above the Reptilia phylogenetic progress appears to travel along two slightly diverging lines, leading on the one hand to the birds, and on the other, to the higher mammals. Both these possess retinae of a very high grade of functional efficiency, and, in both, the embryonic stages of formation of the retinal layers follow very closely the primitive plan. It is as well to consider the birds first, though in many ways they show a higher grade of retinal differentiation than do the mammals.

Birds

These show abbreviation of early stages such as occurred in the fish. The marginal layer is not well developed and ganglion cells and nerve fibres begin to appear on the inner surface at a very early stage. Fig. 17 shows the earliest stage at which ganglion cells can be recognised. They lie on the surface of the neuro-epithelium. Their nuclei are round and they do not as yet show any axons.

They differentiate rapidly, as can be seen in Fig. 18. At this stage the following layers can be recognised from within outwards.

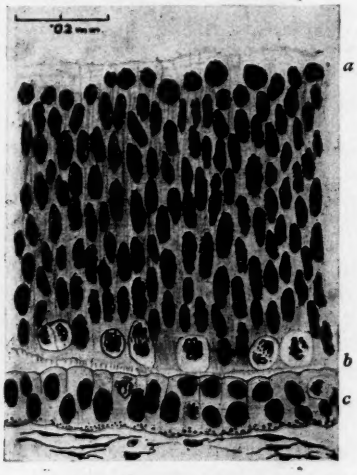


FIG. 17.

Retina of chick embryo of 3 days.

a = early ganglion cells.
b = proliferating layer.
c = outer wall of optic cup.

1. An internal limiting membrane forming by fusion of the ends of the Müllerian fibres.

2. A narrow marginal layer becoming filled up with axons of ganglion cells.

3. A layer of nuclei representing the inner neuroblastic layer. The cells in this layer are of two sorts, namely ganglion cells and supporting cells. The ganglion cells are easily distinguished.

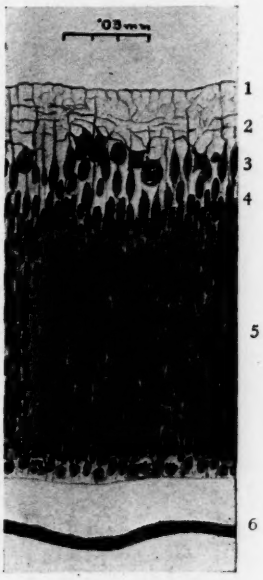


FIG. 18.

Retina of chick. For numbering of layers see text.

They are multipolar and their processes can often be traced some little distance. The axon enters the nerve fibre layer. The supporting cells have oval undifferentiated nuclei and an elongated cell body arranged at right angles to the direction of the layer. This is prolonged into an inner and an outer process, the former running through the nerve fibre layer to its inner surface and representing the inner limb of a Müllerian fibre, and the latter passing outwards to be lost among the cells of the outer neuroblastic layer.

4. A narrow interval (the transient fibre layer) separating inner from outer neuroblastic layers.

5. The outer neuroblastic layer, composed of many superimposed rows of undifferentiated oval nuclei, the deepest row of which is undergoing mitosis.

6. The pigment layer (outer wall of optic cup). This has no processes as yet.

This stage shows very clearly the origin of the Müllerian fibres from the outer neuroblastic layer.

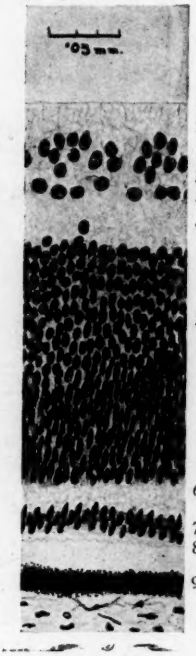


FIG. 19.

Retina of chick. For numbering of layers see text.

The next stage of interest is that seen in Fig. 19.

The structures seen will be considered *seriatim* as before:—

1. An internal limiting membrane.

2. A nerve fibre layer.

3. A layer of ganglion cells and Müllerian fibre nuclei (the latter not so easily seen now, as they are farther apart). The outermost row of the ganglion cell nuclei are becoming separated from their fellows by a very narrow interval (3*a* in the figure), which is the forerunner of the inner molecular layer. This single row of cells (3*b*) is that of the future amacrines, just beginning to separate out from the rest of the inner neuroblastic layer.

4. The transient fibre layer, wider and free from nuclei.

5. A thick band of nuclei, the inner rows of which are differentiating and are round, while the outer ones are still oval. This band represents the major part of the outer neuroblastic layer. The cells of it will form bi-polar cells later.

6. A narrow interval, the outer molecular layer.

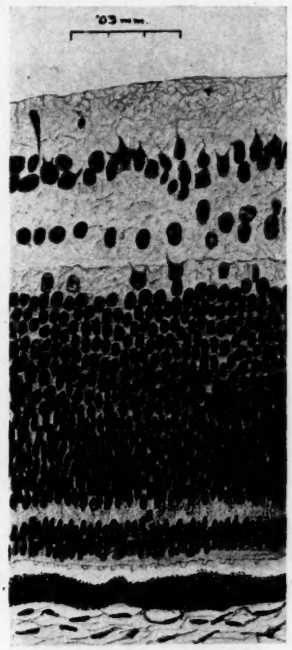


FIG. 20.

Retina of chick. Numbering of layers as in Fig. 19 and text.

7. Two rows of nuclei derived directly from the proliferating cells of the previous stage and destined to form the rod and cone nuclei.

8. An external limiting membrane, showing small projections, the beginnings of the visual elements themselves.

9. The pigment layer.

After this stage the row of amacrine cells and also the Müllerian fibre nuclei become separated from the ganglion cells and begin to fuse with the bi-polar layer, thus bringing about a widening of the inner molecular layer and a narrowing and final disappearance of the transient fibre layer of Chiewitz. Fig. 20 shows this change

in progress. In it the amacrine cells form a distinctly separate layer and the layer of Chiewitz already contains a few nuclei in transit. The layers are indicated in the figure by the same

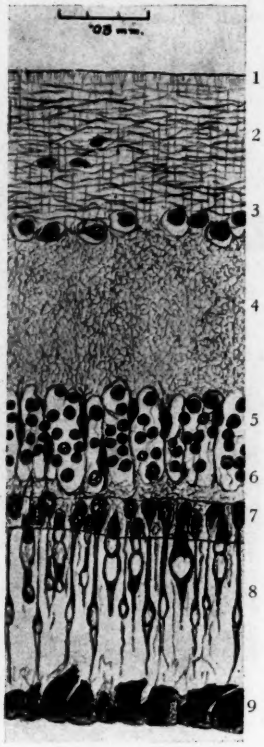


FIG. 21.

Retina of hen.

1 = internal limiting membrane.
2 = nerve fibre layer.
3 = ganglion cells.
4 = inner molecular layer.
5 = inner nuclear layer.
6 = outer molecular layer.
7 = outer nuclear layer.
8 = rods and cones.
9 = pigment epithelium.

numbers as in Fig. 19. Finally the layer of Chiewitz completely disappears and the adult condition is reached as in other species by the narrowing of the nuclear layers and the widening of the fibrillar zones consequent on the general enlargement of the eye. Fig. 21 shows the process complete, even to the development of flame-shaped processes in the pigment layer.

Mammals

We have seen in birds an even clearer demonstration of the derivation of the various cell layers according to the basal vertebrate plan. They furnish by far the most convincing material for the study of the amacrine cells and the formation of the transient fibre layer, even though there is abbreviation of early stages. In the mammals, on the other hand, the early stages are very clear

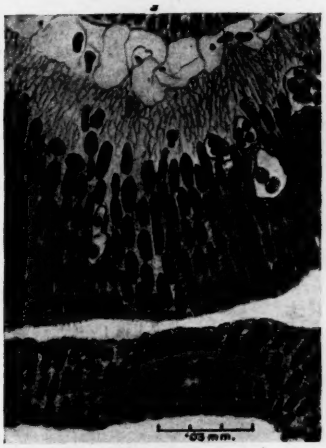


FIG. 22.

Section through both walls of the optic cup of a human embryo of 5 mm.

a = marginal layer.
b = capillary.

cut, but the later stages tend to become somewhat slurred. In addition another process becomes apparent, namely, a transient vascularisation of the retina in early stages. In all the animals below the mammals the wall of the optic cup is completely avascular throughout the period of cellular rearrangement which we have been studying. In some mammals*, however, the beginning of differentiation seems to be accompanied and possibly to some extent initiated by a penetration of small blood-capillaries into the inner wall of the optic cup from its inner surface. This is merely part of a general capillary vascularisation of the wall of the nerve tube at this stage and is in no sense peculiar to the region of the optic vesicle. It is extremely transient, the capillaries (which

* Man and the mouse only have been available for investigation, so that nothing definite can be said of other species.

only involve at their maximum development the lower part of the invaginating optic vesicle) disappearing as soon as the distinction between inner and outer neuroblastic layers is established. This initial peculiarity of the developing mammalian retina is probably to be looked on as an expression of the great vascularity of the eye

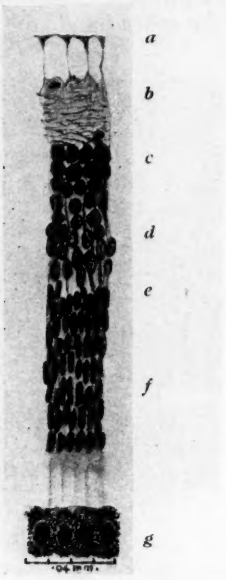


FIG. 23.

Section through the retina of a human embryo of 21 mm.
a = fibres of Müller forming internal limiting membrane.
b = nerve fibre layer.
c = ganglion cells, *d* = amacrine cells } inner neuroblastic layer.
e = transient fibre layer.
f = outer neuroblastic layer.
g = pigment layer.

region throughout the whole of the organo-genetic period, which is one of the distinguishing features of the mammalian embryo.

In other respects the appearance of the retinal layers in the mammals follows the vertebrate plan so far seen to hold good, with modifications, for representatives of all the other classes. We can consider briefly some of the more important stages as seen in human embryos.

Fig. 22 shows the stage of vascularisation described above and also emphasises the fact that there is no abbreviation of early

stages. A well-formed marginal layer is present before the distinction between inner and outer neuroblastic layers has begun. The formation of the inner neuroblastic layer by migration of the innermost nuclei into the marginal layer is in man exactly similar to that seen in the reptile Chrysemys marginata (Fig. 13) and need not be figured. The derivation of the amacrine cells from the inner neuroblastic layer is seen in Fig. 23. It will be noted that

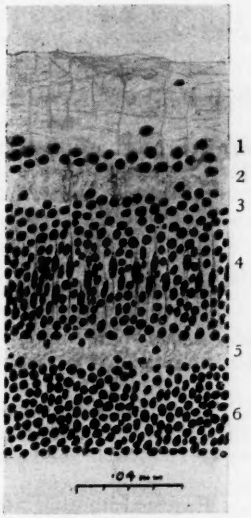


FIG. 24.

Section through the retina of a five and a half months human foetus.

1 = ganglion cells. 4 = bi-polar and Müllerian fibre nuclei.
2 = inner molecular layer. 5 = outer molecular layer.
3 = amacrine cells. 6 = outer nuclear layer.

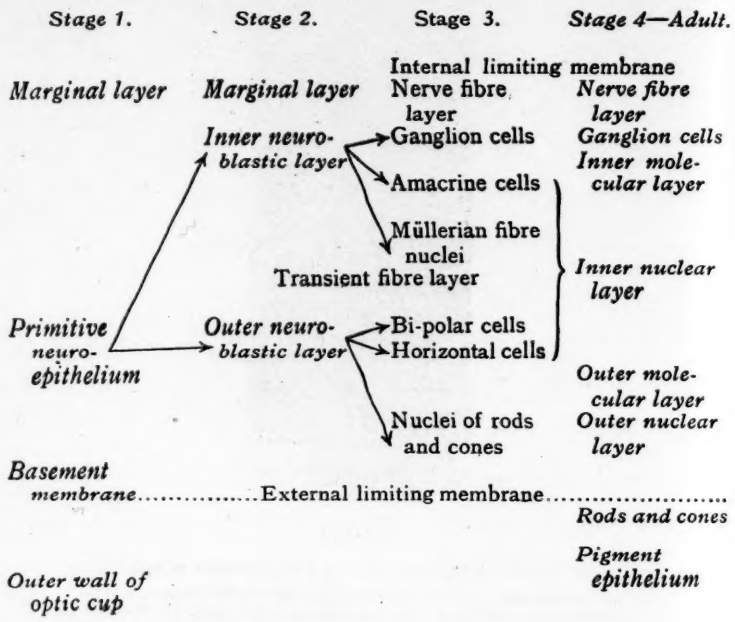
fibres of Müller are well marked and that the distinction between the ganglion cells and the amacrine cells is marked by difference of staining and of position, though together they constitute a single layer. The position of the transient fibre layer of Chiewitz is apparent, but it is not a true layer as in birds. It is of note, however, that, in the human macular region, the layer of Chiewitz attains a development equal to that seen in birds and can be studied as easily. Over the rest of the human retina it is only present as a line of separation, not as a true layer.

Fig. 24 shows the formation of the inner molecular layer by fusion of the amacrine cells and nuclei of fibres of Müller with the

bi-polar layer. It also shows the development of the horizontal cells from this layer.

At this stage (5½ months) the layers are complete though their thickness and appearance have not reached the definitive condition. Development of the macular region is retarded and does not cease until after birth.

We can thus, by inclusion of the human type, formulate a final scheme of differentiation of the vertebrate retina, thus:—



In this scheme the stages in italics (1, 2 and 4) are those which can also be traced in the Cyclostomes. It will be seen that evolution has merely resulted in a visible sorting out (Stage 3) of cells which even in the lower orders are probably functionally distinct. No essential alteration in the plan has occurred.

Before leaving the subject of retinal differentiation one must consider the means whereby, though constantly adhering to the same anatomical plan, the phylogeny of vertebrates has resulted in a very marked scale of physiological evolution. The factors concerned in this are three. The first, and most important, is the co-incident elaboration of the central nervous system, allowing of increasingly complex reactions to the stimuli received through the

percipient end-organ of the retina. This alone will go a long way to account for the high grade of efficiency of so primitive an organ as we have seen the human retina to be. It need not be dealt with further here.

The second factor is the slow but definite and steady tendency throughout phylogeny towards an increase in the number of percipient elements in a given area. This of course allows of increase in visual acuity since an increasing number of points on an object can be perceived as distinct. The process involves not only a greater concentration of percipient elements in a given area, but also to a less extent a diminution in the size of the individual elements themselves. For example, if we look at the cones in Petromyzon we see that each cone measures approximately 0.006 mm. across, and that there is a gap of 0.004 mm. between the adjacent cones. Therefore, in a strip of retina 1 mm. long and 0.01 mm. wide, there would be only 100 cones. In the amphibian retina, a decrease both in size of visual elements and in the gaps between them is apparent. The approximate measurements in the retina of a fully grown frog were :—

Average thickness of individual elements	= 0.005 mm.
Gap between adjacent elements	= 0.003 mm.
Total number of elements in a strip of retina 1 mm. × 0.01 mm.	= 125

In the Sauropsida the decrease in size of the elements and of the gaps between them is further apparent: thus, in a hen's retina, near the posterior pole, the measurements were :—

Average thickness of individual element	= 0.003 mm.
Gaps between adjacent elements	= 0.0025 mm.
Total number of elements in a strip of retina as above	= 327

In the macular region in man the increase in number is brought about by still further reduction of the gaps, so that the adjacent cones are in apposition, the size of the cone remaining little changed, giving the following result :—

Diameter of cone at the macula ...	= 0.004 mm.
Gaps between cones	nil.
Total number of cones in strip as above	= 652

The third factor in the phylogenetic improvement of the eye is the tendency towards specialisation of areas of acute vision, which begins to appear above the reptiles, and which makes possible on the one hand the elaborate arrangements of birds, and on the other, the macula lutea of man. These areas of acute vision are very varied in size and shape. In some of the lower mammals they are

merely represented by broad areas having a slightly higher functional activity than the rest of the fundus. In birds they are still further elaborated, reaching a stage which surpasses that seen in man. The shape, size and number of maculae present in an avian eye varies with the species, but in many instances there are both nasal and temporal maculae in each eye, and in some cases these are connected by a specialised band-like area, which presumably gives clear definition over a continuous strip of the field of 90° or more. In man the structure of the macula is well known. It is worthy of note, however, that its differentiation resembles that found in the avian retina rather more than does the differentiation of the more peripheral parts of the human retina. There seems some ground for supposing that the clear cut developmental differentiation of the amacrine cells which accompanies a high degree of development of the transient fibre layer of Chiewitz is associated with a final high grade of functional activity. It is also suggestive to note that the amacrine cells are developmentally more important and more closely linked with the ganglion cells than would be thought from their study in the adult only.

Conclusions

From the foregoing examination of the process of differentiation of the layers of the vertebrate retina we can distinguish an underlying principle which remains unchanged, as well as an evolutionary scale of modifications superimposed on this.

From a study of the general principle it is apparent in every case :—

(*a*) that the ganglion cells are the first to differentiate;

(*b*) that the amacrine cells are intimately associated with the ganglion cells and only secondarily separated from them;

(*c*) that the inner nuclear layer is a complex layer containing elements derived from both the primitive retinal layers (*i.e.*, the inner and the outer neuroblastic layers);

(*d*) that the percipient elements themselves are the last to differentiate.

From a study of the secondary modifications we see :—

(*a*) that supporting tissue differentiates relatively late in phylogeny.

(*b*) that abbreviation of stages can occur without modification of the general plan;

(*c*) that throughout phylogeny there is a tendency to improvement of function by

1. crowding together of percipient elements,
2. development of special areas of acute vision, the differentiation of which, however, always follows the original general plan.

THE EARLY DEVELOPMENT OF THE ENDOTHELIUM OF DESCEMET'S MEMBRANE, THE CORNEA AND THE ANTERIOR CHAMBER OF THE EYE

BY

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ASSISTANT OF THE UNIVERSITY EYE CLINIC, AMSTERDAM

"IN so far as embryology is concerned, ophthalmology forms a happy and notable exception to the general trend of modern medicine towards intense specialisation. Instead of being of semi-detached and somewhat academic interest, embryology has taken a real and integral share in the clinical applications of ophthalmology, and the greater part of recent research on ocular formation and growth has been undertaken by ophthalmologists working with the solution of clinical problems as their ultimate aim

This clinical interest with which embryological questions are associated is accounted for by three factors. In the first place, recent improvements in the methods of examination of the living eye have rendered possible the recognition of its individual structural variations with a greater minuteness than is possible elsewhere, and the explanation of many of these is purely embryological. Moreover, the diagnosis of congenital from acquired conditions is frequently more difficult and important in the eye than elsewhere in the body, and decisions upon many questions of importance can only be made in the light of a knowledge of normal and abnormal development. Finally, both morphological and physiological problems may be considerably clarified in many cases by an appeal to the ontogeny of the phylogenetically related species." (Duke-Elder).

The endothelium, first mentioned by Pappenheim in 1842, is becoming of increasing clinical importance, especially since the discovery of the slit-lamp, and on that account Professor Zeeman urged me to study these cells, beginning with their embryology. Material and literature proved very interesting, not least with respect to the cornea and the anterior chamber of the eye, the development of these being inseparably connected with that of the endothelium. An exact knowledge of the embryology of a certain cell or organ is of importance for the understanding of adult structures, and of physiological and pathological phenomena. This rule must be specially emphasised for the endothelium of Descemet's membrane. In the first instance its development is the only argument for the name endothelium. And though, *e.g.*, after Ranvier and Virchow, it is spoken of as an epithelium because of its histological qualities, in recent literature the name endothe-

lium is generally accepted. Secondly, the development leads to the denial of any relation of these cells with higher differentiated cells of mesodermic origin, as, *e.g.*, the epithelium cells of the tubuli of the kidney, or to the classification of them automatically in the group of the endothelia. So, *e.g.*, Terrien says: "Leure nature endothéliale cependant n'est past douteuse et est démontrée par le développement." The ophthalmologist concludes that these cells must be of a rather indifferent character, and line a cavity. And really, this is the only meaning of the term endothelial nature, as becomes evident in studying the literature on this subject.

This development is described by Howden in Cunningham's Text book of Anatomy as follows: (*comp.* Fig. 1, human embryo 26 mm.)

"The condensed mesoderm surrounding the optic cup becomes the sclera and the choroid. In the portion of mesoderm in front of the lens a cleft-like fissure appears, and divides it into a thick anterior and a thin posterior layer. The former becomes the substantia propria of the cornea, the latter the stroma of the iris and the anterior part of the vascular tunic of the lens (pupillary membrane). The fissure represents the future camera oculi anterior and its lining cells form the endothelium of this chamber."

Thus the anterior chamber is simply a cleft in embryonic mesoderm, comparable with the lymph-spaces in the skin of Anura (Nussbaum) appearing in about the second month of embryonic life. The cells lining this cleft anteriorly form the endothelium of Descemet's membrane. This theory as given in most modern text books and even recent publications (I. Mann, 1925), is modified by German authors (Brückner, Wolfrum, Seefelder), who especially paid attention to the later stages and showed that the anterior chamber is virtual first and filled much later (fifth month), first in the periphery. The anterior pole of the lens (covered by the pupillary membrane), remains in contact with the endothelium until about the sixth month. They believe that the anterior chamber of Koelliker is a result of fixation. Keibel and Lindahl[4] oppose this view, and claim to have embryos undoubtedly showing a real, filled anterior chamber in these early stages. It is interesting to note that the same controversy existed 40 years ago (Krishewsky). It is to be noted, however, that the mode of development of the cornea, pupillary membrane and the endothelium is exactly the same in both theories.

In 1926 Seefelder[5] described a thin layer of mesodermic cells behind the epithelium, which he considers to be the endothelium. He believes that first the endothelium appears behind the epithelium as a compact layer, the cornea-stroma cells secondarily growing in wedgewise between epithelium and endothelium. The

pupillary membrane is seen only later and is claimed to be at its first appearance in a thin ectodermal lamella, differentiated in the "anterior vitreous body." The relation of stroma-cells and endothelial cells, described in an earlier publication (Fig. 21, page 3882, American Encyclopedia, 1914, Plate XXV; atlas of Bach and Seefelder, 1911) is denied now and considered to be a result of fixation (wrinkling of the cornea). This entirely different mode of development is claimed to be found only in man; in mammals Koelliker's description should be maintained. It seemed to me that this last suggestion was very improbable indeed.The general outline of the development of the eye, not only in mammals, but in the whole class of vertebrates shows such a striking similarity, that Froriep says: "Wie Athene aus dem Haupte des Zeus tritt das Vertebratenauge in die Erscheinung." Moreover, not a minor detail is concerned here, but the very principle of the construction of the anterior part of the eye. Further, I could not understand why Seefelder's finding in 1926 should consequently lead to a correction of his former publication. The picture as given in Plate XXV of the Atlas (Fig. 21, page 3882 of the American Encyclopedia) is very difficult to explain by wrinkling, and it seemed much more simple and probable that the first layer of mesodermic cells appearing behind the epithelium (1926) is the matrix for both endothelium and stroma-cells. So it had not been necessary to recall the intimate relation between stroma and endothelial cells shown in Plate XXV.

The supposed remarkable isolated position of man, the dominating rôle of the endothelium, the claimed subconjunctival origin of the cornea-stroma after Seefelder, the non-existence of an anterior chamber in earlier stages, the rôle of the anterior vitreous body, the existence of which is even denied by Dejean in 1925, each of these indicates a problem, together showing that the fundamental facts of the development of the anterior part of the eye are still obscure. So we find here an unexpected and promising field for research, unexpected, as Duke-Elder says in 1927: "The general outline of the development of the human eye has long been known and the scope for further research lies entirely in the direction of a minute study of the few details which still remain obscure in the main plan." This gap in our knowledge becomes evident in the difficulties we meet in the explanation of congenital corneal opacities (Mann, 1927).

Now I shall describe my own observations, at the same time discussing the principal studies as far as they have actual value. I am much indebted to Prof. Bolk of Amsterdam, and Dr. de Lange of Utrecht, for lending me the material.

Only in a few series this extremely vulnerable anterior part of the eye was sufficiently preserved, especially in the human material

that I studied first. And even in the majority of these series the central part of the cornea was seriously damaged, or had even completely disappeared. In nearly all series the plane of section was not conducive to a clear understanding. The result of these facts is, that in many publications sections through the periphery of the anterior chamber have been studied, such a section (Fig. 1)

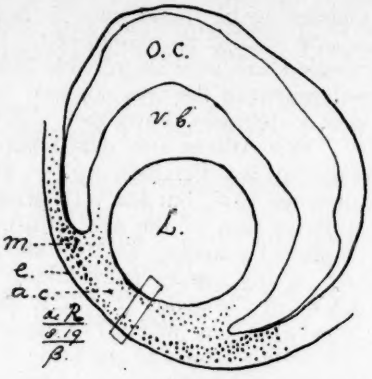
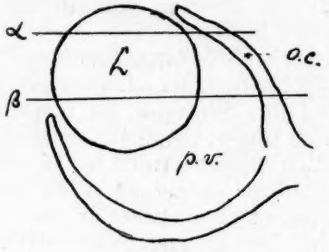


FIG. 1.



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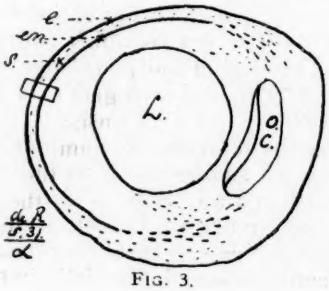

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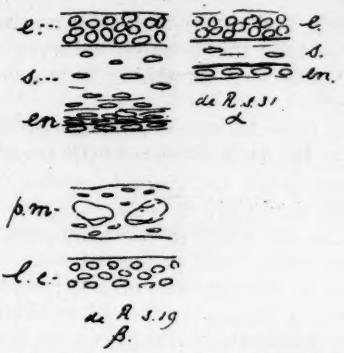

FIG. 4.—Human embryo of 26 mm.

apparently giving a convincing picture in favour of Koelliker's theory. (Compare Fig. 2, section through model in wax after Born of the same embryo, section β).

A higher magnification of the section of Fig. 1 (human embryo of 26 mm.) shows, however, in this well preserved embryo, that cornea and pupillary membrane already are in a high stage of development (Fig. 4β). This different structure of cornea and pupillary membrane is not visible in the majority of the embryos, and so the theory arose of a cleft in still undifferentiated post-epithelial mesoderm.

In section (Fig. 3) going through the centre of the cornea, compare Fig. 2, section α where only a small part of the optic cup is seen. Here we find that the cornea is remarkably thin, consisting of an epithelium and an endothelium with only a thin layer of stroma-cells between them. But here, apparently, we find no trace of a pupillary membrane before the anterior pole of the lens, and so it is evident that the pupillary membrane in this embryo is not yet complete over the centre. This makes it very probable that Seefelder was right when he described in 1911 that first the cornea appears, while the pupillary membrane is seen a little later only.

The problem, whether stroma and endothelium are differentiated from one matrix or not I could study in a slightly younger embryo (human embryo of 22 mm.). I was glad to find that indeed over the centre, the cornea apparently consisted of two very distinct layers: an epithelium and an endothelium, while at the periphery the stroma-cells were sandwiched between these two layers. This seemed to be a confirmation of Seefelder's theory (as stroma and endothelial cells seemed to be independent from one another), though by no means a proof, as it still remained possible that the so-called "endothelium" was nothing but the matrix for the

definite endothelium and the stroma-cells as well. Moreover, to increase the difficulties in this younger embryo, behind the cornea, even in the centre, was seen something very much like a damaged pupillary membrane.

Thus the human material was insufficient on which to come to a definite conclusion, but this only made the problem more interesting as it had been amply sufficient to render Koelliker's classic theory at least very doubtful.

The next step was the study of the mammals, and fortunately I had a vast and unusually well preserved material at my disposal.

Plate 5 is a section of an embryo of *Roussetus* (cat). The space between lens, margin of optic cup and epithelium (surface ectoderm) is filled with a delicate fibrillar network, the anterior vitreous body, continuous with the posterior vitreous body by the isthmus.

FIG. 5.—Embryo of *Roussetus*.

The existence of an anterior vitreous body, that seemed doubtful in the human material, was proved here with an absolute certainty, and Dejean is certainly wrong in denying its existence. At the same time, however, I must point to the fact that this delicate tissue was found so distinct only in one series among the many I studied in this group. A few mesodermic cells have already grown in behind the epithelium, but practically no nuclei are seen in the anterior vitreous body.

The best series for later stages was furnished by the *Tarsius* material (lemur, half-ape); some of them are described in the "Normentafeln of Keibel and Mall." We find (Fig. 6) that very soon (*tarsius* embryo of 10 mm.) the layer of mesodermic cells behind the epithelium becomes complete over the centre as well; this is the endothelium of Descemet's membrane, as later stages show. In the centre of the future cornea this layer is situated directly posterior to the epithelium. Laterally, however, it bends away from the epithelium, leaving an "open corner" between both layers in which minute fibrils can be traced. Laterally this "open corner" is fenced off by mesodermic cells. These are lying further apart and stain less darkly than the endothelial cells. They

are lying close to the epithelium as well as to the mesodermic cells surrounding the bulbus, so that there is not the least sign of shrinking here. This makes it very probable that the "open corner" is not due to shrinking; moreover, it is found in the same way in different embryos, and the description of older stages will show that it plays its rôle in the mechanism of the development of the cornea.

In considering the photography of the "open corner" one is struck by the curious fact that the endothelium is marked off anteriorly so perfectly sharply that its limits at the side of the endothelium are as definitely lined out as they are at the side of

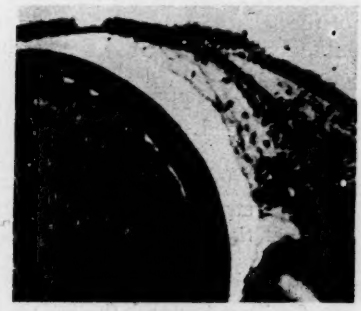

FIG. 6.—*Tarsius*, 10 mm. embryo.

the epithelium. In somewhat older series a higher magnification shows, however, that the regularity of the anterior border of the endothelium is not surprising as the endothelium appears to be limited anteriorly by a very distinct membrane very much like the basal membrane of an epithelium (*tarsius* embryo 13 mm.)

But also at the side of the lens and the optic cup the post-epithelial layer of mesodermic cells, which I called a little rashly endothelium, is marked off sharply as the anterior from the posterior part of praelenticular mesoderm. This posterior part is a fibrillar network, rather coarse in comparison with the numerous minute fibrils of the anterior vitreous I described in a younger stage. However, this fibrillar tissue (Fig. 6) must be a derivate from this anterior vitreous (Fig. 5). The beautiful studies of v. Szily about the embryonal connective tissue allow us to understand what has happened here. At its first appearance the anterior vitreous undoubtedly is of ectodermal origin. It originates from basal cones of the epithelium of the lens, of the margin of the optic cup

and of the surface ectoderm. At the same time, or a little later, as the endothelial cells grow in behind the epithelium (surface ectoderm) as a compact layer, other mesodermic cells, though in a moderate number, invade the anterior vitreous, taking over the nourishment of its fibres. Under its influence the anterior vitreous changes its original aspect, the fibres becoming much thicker. To Virchow, living in the area of the doctrine of the absolute specificity of the germ-layers, such an explanation would have been unacceptable. However, not only v. Szily's investigations, but also those of a great many other competent authors showed that the validity of this doctrine is not absolute. This is generally accepted nowadays.

The loose postendothelial fibrillar tissue is very vulnerable, and it easily shrinks together. So in photograph 6 it is detached from the surface of the lens and the space between it and the lens seen here is undoubtedly due to shrinking. If it loses its connection with the endothelium as well, it shrinks together as is seen in nearly every human embryo. This is also the case in the second human embryo I mentioned. Without a knowledge of the development in *Tarsius*, though unwillingly, we had to take this remainder for a damaged pupillary membrane, but without any doubt it is the greatly retracted fibrillar postendothelial tissue. Herewith is explained at the same time why Keibel and Lindahl insist so much on the existence of an anterior chamber in these very early stages, as it is clear that, being a result of the shrinking of this delicate fibrillar postendothelial tissue, such an artificial "anterior chamber" is found with the greatest regularity. *Thus we are safe in concluding that in very young stages there is not yet an anterior chamber of the eye.*

With the development of the endothelium the anterior boundary of the future anterior chamber of the eye is completed. Now we have to see if there are any traces of the posterior boundary, the pupillary membrane. And indeed, in the embryo of Fig. 7 (*Tarsius* embryo of 13 mm.) we see laterally a distinct membranous pupillary membrane. Most of the cells lying on its anterior surface (apparently directly on the lens epithelium) are torn out of the endothelium, as other sections prove. Indeed, in this stage of development, only a few mesodermic cells have grown in on the anterior (distal) surface of the pupillary membrane, and at its periphery only, it being still membranous over the centre. In this stage there is a slit-like fissure between the basal membrane of the epithelium and the membrane limiting the endothelium anteriorly. This latter membrane is now very distinct. In most places, of course, it is seen in sectional view here and there, after twisting 90 degrees in front view, however, so that there can be no doubt as to its being a real membrane. This membrane absolutely

shuts off the endothelium from the fissure anterior to it. In this fissure between the two membranes minute fibres can be traced. The thickness of the layer sandwiched between the two membranes increases as the posterior membrane bends away from the basal membrane of the epithelium forming the "open corner," and here the very delicate structure of this inter-membranous tissue becomes more obvious. However, in this stage only the apex of the "open corner" is filled with it. The cells I described

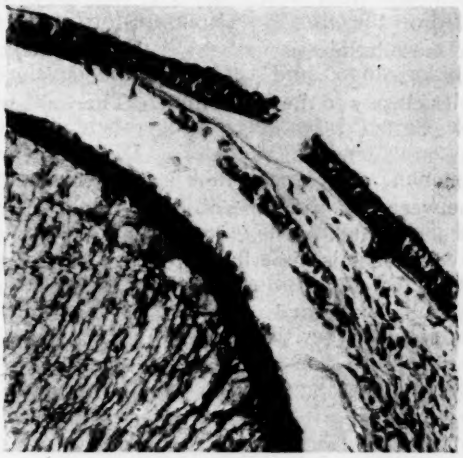

FIG. 7.—*Tarsius* embryo of 13 mm.

before, forming its lateral wall in younger stages, have invaded the "open corner" and filled it up, except at its apex, with oblong or long stretched nuclei. These stain less darkly and are lying further apart than the endothelial cells. In their internuclear substance thick fibrils appear chiefly parallel to the epithelium. Obviously these are the cells afterwards forming the stroma of the cornea. And indeed the arrangement in slightly older embryos is as follows (comp. Fig. 4). Behind the epithelium is seen a distinct basal membrane, then follows a thick layer of loose connective tissue, nuclei and fibres arranged parallel with the epithelium: the stroma; then again a distinct membrane and then the endothelium. The basal membrane of the endothelium cannot be traced in still later stages so that I believe this is not Descemet's membrane, this membrane being a product of the endothelium and only

seen later. The basal membrane of the epithelium is distinct in older embryos as well, so that I believe it is Bowman's membrane itself.

Thus it is proved that the first mesodermic element of the cornea is the endothelium of Descemet's membrane, and that this endothelium is absolutely independent of the corneal stroma cells.

The only embryological argument to speak of an endothelium must be abandoned; on the contrary, the independent and very early development, and the striking epithelial aspect, especially in the young stages of embryonic life, forces us to consider these cells as a mesodermal epithelium as Ranvier and Virchow previously did on the histological features of the adult cells.

The loose mesodermic tissue behind the endothelium atrophies rapidly in older stages and very soon the developed pupillary membrane lies closely to the epithelium. The walls of the anterior chamber are formed, the anterior chamber, however, between endothelium and lens is virtual as Wolfrum and Seefelder described in man. The space in Fig. 7 is undoubtedly due to shrinking between endothelium and lens. Herewith we arrived at a period of development where as far as I know the different authors agree, and it is superfluous to study older stages.

As the reader will have realised already, the study of the *Tarsius* material has fully explained the difficulties met with in man, the photographs speaking for themselves. The membranes allowing a definite decision are seen in a few of the very best *Tarsius* series only, and consequently are seldom visible in man. It is evident that the development in *Tarsius* is exactly the same as it is in man.

I then studied other mammalia, sheep, horse, pig, rat, mouse, rabbit, etc., the usual objects for embryological studies, the material that gave birth to Koelliker's theory and that induced Seefelder to postulate the supposition of the isolated position of man. I shall discuss these series later and describe my investigations on the birds next, a quite different group of animals in its general features. Thus, *e.g.*, the pupillary membrane here seems to be missing.

The birds have a great historical value for our problem, as to my astonishment the principle of the development of the anterior chamber of the eye as seen in man and *Tarsius*, was described already in birds in 1877 by Kessler[3]. I shall quote here his original description, as his publication is rather difficult to obtain: "An der Innenfläche des Hornblattes (Epithelium) erscheint eine schmale structurlose Schicht. Kaum hat diese die Dicke des Hornblattes erreicht-etwa um die Mitte des 5en Tages, so drägen sich die Koofplatten (Mesoderm) zwischen den peripherischen Teil der Anlage der Cornea und der äusseren Lamelle der secun-

dären Augenblase hindurch, bis an die vordere Augenkammer. Von hier aus kriecht dann eine von vornherein einfache Zellenschicht an der Innenfläche der Anlage der Cornea propria, concentrisch vorrückend gegen den Mittelpunkt dieser Fläche hin. Am 6en Tage treffen die Zellen von allen Seiten her in demselben zusammen und damit ist das innere Epithel der Cornea (Endothelium) fertig hergestellt. Von dem äusseren Teil der Kopfplatten aus beginnt so bald die Bildung des inneren Epithels vollendet ist, eine Einwanderung von Zellen in die strukturlose Schicht."

Kessler tried to give his theory a more general signification, as Lindahl tried to do later, but did not succeed, and it was plainly rejected by Nussbaum in the Graefe-Saemisch Handbuch. Nussbaum certainly did not study birds himself. If he had done so he would have added that in birds indeed the endothelium originates very early, as Angelucci and Hertwig admit. Indeed Kessler's theory in birds has found the most complete confirmation by Knape[3], Lindahl, Slonaker, Lagueusse. Of these interesting studies I shall only discuss Knape's here.

In an embryo of chicken, 2½-3 days old, Knape gives a detailed description of the anterior vitreous, which is very well developed here. In this delicate fibrillar network appears a membrane parallel to the epihelium, that Knape calls a "Richtungshäutchen." As he observed in later stages posterior to this membrane the endothelial cells grow in, the membrane obviously directing the course of the cells. This "Richtungshäutchen" (directing membrane) undoubtedly must be homologous with the prae-endothelial membrane we found in *Tarsius*. In *Tarsius* there is a slit-like fissure between this membrane and the basal membrane of the epithelium. I remarked that this was probably caused by the development of a delicate tissue sandwiched between the prae-endothelial membrane and the basal membrane of the epithelium. In birds this tissue evidently reaches a high degree of development, so that finally in later stages it becomes as thick as the epithelium, only then the stroma cells grow in in this tissue as described in *Tarsius*.

After Knape this tissue is still a part of the anterior vitreous, its fibres originating from the basal cones of the epithelium cells, after other authors it would be homologous with the corium of the skin; it would take too far to discuss this detail here. This tissue is mentioned by Kessler already as the "hyaline layer."

Knape's description of a "Richtungshäutchen" has not been confirmed up till now, and in studying my material the reason was easy to find. The demonstration of this membrane was very difficult, it merely seems to be the posterior border of the "hyaline layer," and not an independent membrane. However, I must confirm Knape's view, as in many young series I have seen this

membrane, insufficiently definite, however, to make a good photograph. Knape's investigations induced me to view this problem in quite a different way. They opened a perspective that Knape obviously did not realise. If the "Richtungshäutchen," differentiated in the anterior vitreous, and really is primary to the endothelium and a derivate from the ectoderm, this would mean that the principle of the construction of the anterior part of the eye is given by the ectoderm, the mesoderm being only of secondary importance, a most fascinating conception fully in accordance with general recent experimental embryological results.

After Knape the anterior border of the iris is indicated at its first appearance by a thin lamella in the anterior vitreous and I can fully confirm his observations. Like this author, I find this membrane continuous over the surface of the lens, and consider it as homologous with the pupillary membrane in mammals. Thus it is very probable that the membrane preceding the cellular pupillary membrane in *Tarsius* is also of ectodermal origin. Seefelder found this membrane in man and also believes it is of ectodermal origin.

So we find that the principle of the development of the eye in birds is exactly the same as it is in man.

The next step was the study of the Amphibians.

Knape described, in the capacious space between lens and ectoderm of a young embryo of *Rana temporaria*, an anterior vitreous, which, contrary to other species, shows only few fibres. In this tissue there appears a lamella in front of the lens. A week later the endothelium grows in behind this lamella (Richtungshäutchen) and already forms a compact layer at the time that only a few stroma-cells grew in, also exactly the same mode of development as described in other groups. This, however, is not absolutely right. Here indeed, in a very young embryo I could find the development of a "Richtungshäutchen" with convincing distinctness, the endothelial-cells however growing in very early, and not as a compact layer.

In a slightly older stage the optic cup is fenced off anteriorly by a rather thick membrane. At its posterior surface the endothelial cells now are very flat. Between this membrane and the epithelium there is an uncommonly wide space with little or no structure. In later stages the membrane gets thicker, and cells can be traced on its anterior surface as well. There persists, however, a wide space between it and the epithelium. Here we have reached the stage where Giesbrecht begins his complete and detailed report of the development of the eye in *Anura*, induced by Wachs' and Harms' discovery, who for the first time described in these tadpoles freely movable eyes under a transparent "Brille." Only the recent experimental-embryological work brought this fact to

light, that our modern histological methods had been unable to detect. Thus the wide space between eye and 'Brille" is not a result of shrinking as former authors believed (Fig. 8) (embryo of *Bombinator,* L2).

Giesbrecht[1] describes the further development in *Anura* as follows: Afterwards there is a distinct inner endothelium, the membrane has thickened and now is called "tunica propria sklerotica, Sklerallamelle" with an outer "endothelium" the latter two chiefly consisting of fibrillar tissue. The "Brille" consists of an epithelium, a "tunica propria cutanea," continuous with the basal-

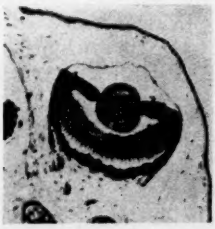

FIG. 8. *Bombinator* embyro.

membrane of the epithelium of the skin and an inner "endothelium." Even in older embryos this tunica propria cutanea contains only a few cells, but has much increased in thickness; the same is the case with the tunica propria sklerotica. The fissure between "Brille" and "Sklerallamelle" is first filled up with fluid, allowing free movements of the embryonal eye; afterwards, in metamorphosis, subcutaneous and orbital connective tissue cells grow between "Brille" and eye, so that the solid adult cornea is formed, thus making the eye immovable.

If possible, this peculiar mechanism of development of the adult amphibian eye emphasizes still more the close relation of the endothelium and its basal membrane ("Richtungshäutchen") with the optic cup. One might say this is the eye-unit, primitive eye; the mechanism of transformation of the skin before the eye is, though very important, a secondary process, not directly asssociated with the construction of the eye as an organ of sense, only allowing the communication of this organ with the outer world. It is clear that I cannot agree with Seefelder, who supposes that there should be a difference in principle between the development of the eye in man and in Amphibians.

Another problem can be discussed much better here, than directly after the description of the human and the *Tarsius* material: Seefelder supposes that the old theory of a choroidal,

scleral, and subcutaneous part of the cornea should be abandoned, this latter being exclusively homologous with the subcutis. Indeed, as I pointed out before, the first stroma cells growing in wedgewise between the two membranes in the "open corner" in *Tarsius* very probably are cells homologous with subcutaneous cells. In a slightly older stage, however, the posterior layers of the cornea show a very distinct continuity with those of the sclera. It is difficult to accept the statement that the stroma of the cornea of claimed subcutaneous origin should gain only secondarily connection with the sclera (Seefelder); moreover, the described development in Amphibians gives a very strong and convincing support for the old theory, as the different parts build-

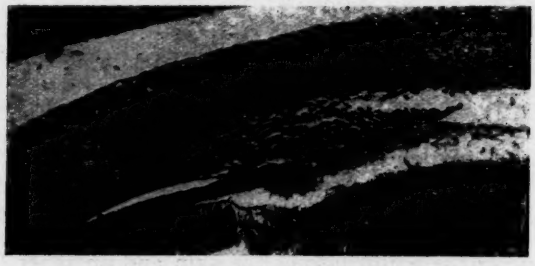

FIG. 9.

ing up the adult cornea before metamorphosis are so absolutely separated. I believe we had better maintain the conception of a cornea consisting of a chorioidal, scleral and subcutaneous (event. orbital) part, but certainly in these young embryos the scleral part is relatively thin.

One of the principal problems still was insufficiently solved. I mean the origin of the basal-membrane of the endothelium, the "Richtungshäutchen." Like Knape, I was convinced, in studying my material, that it must be a condensation in the anterior vitreous; a clear convincing specimen, however, allowing a good photograph has not come to hand. This is no wonder as a cell-free well-developed membrane is seen in a very limited period of life only, in an extraordinarily well preserved embryo, with some good luck in the staining. Thus I decided to study a series of fish as well. Lauber and Froriep deny the existence of an endothelium here, and in a great many series of older embryos it was difficult to judge even if there were any nuclei between the thick lamella forming the cornea. *Petromyzon*, one of the lowest representatives of the class of the vertebrates, showed an arrangement very much like that in amphibians. The "tunica propria cutanea," however, is very

thick, the "sklerallamelle" extremely thin and covered on both sides with a continuous layer of flat cells. There, where this "sklerallamelle" was twisted, one could see the polygonal endothelial cells very distinctly. The posterior surface of the "tunica propria cutanea" is covered with a very well developed endothelium. This "sklerallamelle" is so very thin, that perhaps the name "Richtungshäutchen" would be better. The conception, eye-unit (primitive eye) is very evident again, the endothelium, however, seems to be of less importance here than it is in higher forms. I got the same impression in amphibians where the endothelium is by no means so impressive as it is in birds, *tarsius*, and man in these young stages. The most important specimen that came to hand in this group was an embryo of *torpedo occelata*, which showed such a beautifully developed "Richtungshäutchen," that I am able to give a reproduction of it (Fig. 10). There is very little

FIG. 10.—Torpedo occelata.

shrinking in this embryo, only here and there the anterior vitreous has lost its connection with the epithelium. It is coloured very well and completely fills up the space between epithelium at one side, and lens and margin of the optic cup at the other side, it extends even over some distance lateral to the margin of the optic cup. It is still in direct and absolute continuity with the posterior vitreous, the structure of both being absolutely the same. Fortunately no mesoderm cells had invaded this anterior vitreous body, so that it undoubtedly must be considered as an ectodermal tissue. In this anterior vitreous is seen an uncommonly distinct membrane as the photograph shows: the "Richtungshäutchen" of Knape, which I should like to call cornea primitiva. Thus at a very early moment in the development the anterior limit of the anterior chamber is already clearly fenced off by this ectodermal cornea primitiva. This is the solution of the problem of the mysterious power that forced the endothelial cells to grow in apparently a preformed path in *tarsius*. It is the explanation of the almost improbable fact that an "open corner" could appear surrounded

by cells obviously growing so very quickly in the space between epithelium and lens. Undoubtedly in the very minute network of the anterior vitreous here as well a cornea primitiva was pre-existent to lead the mesodermic cells to their proper destination. I could only demonstrate a "Richtungshäutchen" in *tarsius* in a stage where the endothelial cells had already reached the centre of the cornea. From this point of view an ectodermal cornea primitiva in tarsius is a purely hypothetical structure. If I say, that it is pre-existent here also, I mean that probably a better technique and specimen would show a cornea primitiva here as well, still, undoubtedly the directing power is present. And as the study of the anatomical cornea primitiva in lower vertebrates made its ectodermal nature most probable, this directing power must be of ectodermal nature as well. There we are in harmony with modern views developed by a young branch of science, experimental embryology. Of this recently a report is given by Petersen, who expresses it as follows: The mesoderm is made subservient to the ectoderm ("Das Ectoderm zwingt das Mesoderm in seinem Dienst"). I cannot close this study before describing in a few words the development in marsupial animals, low representatives of the class of the mammals. To my astonishment the situation here was very much like that in birds. Posterior to the epithelium was a well developed "hyaline layer" of Kessler, consisting of rather coarse lamellae, absolutely free from mesodermic cells in the younger stages. Posterior to this layer an endothelium consisting of large, nearly cubical cells was seen, and between endothelium and lens a membranous pupillary membrane. In a rather older embryo the pupillary membrane was vascularised and cellular at the periphery, still, however, membranous and cell-free over the centre, while the cornea was already very thick. It is also very probable that the pupillary membrane in marsupial animals becomes only vascularised and cellular in the periphery, and not in its entire extent, as is the case in other (higher) mammalia. Over the centre it remains membranous as it does over its entire extent in birds.

The last thing I intend to discuss here is the development in Rodentia, etc., the usual objects for research, and to explain further why Koelliker's theory was born, and why it was confirmed so many times. In the first place the anterior vitreous is poorly developed. Then almost simultaneously endothelial and stroma cells enter the praelenticular space in a very young stage and there is hardly any difference between endothelium and stroma-cells Moreover, the loose postendothelial tissue here contains many cells. Membranes are difficult or not traceable. In a somewhat older stage there is a well developed pupillary membrane closely adapted to the endothelium. So, with only a few exceptions, we

find before the lens a number of mesodermic cells, apparently lacking any sign of a differentiation or any arrangement whatever. There often appears an artificial fissure between endothelium and postendothelial mesoderm or between pupillary membrane and cornea: the "anterior chamber" of Koelliker. As, however, I hope to have shown that one great principle governs the building up of the anterior part of the eye in vertebrates, I believe I may conclude that the same principle reigns here also, the more so as the difficulties met with are so easily explained.

I know I have been incomplete, and have not discussed some important problems, as, *e.g.*, the nature of Kessler's hyaline layer, the younger stages in man when a postendothelial loose tissue also is seen, nor have I dealt with the Reptilia. I hope to fill out these lacunae in a detailed description of the individual embryos I studied with a complete review of the literature in a future more extensive study.

Conclusions

1. The same principle governs the building up of the anterior segment of the eye in the whole group of the vertebrates.

2. This anterior segment of the eye is outlined at its first appearance by the ectoderm; the general scheme more or less modified in the different species is as follows:—

(*a*) Cornea: In the anterior vitreous a membrane is formed: the cornea primitiva, posterior to which the endothelium grows in as the first mesodermal element of the future cornea, then the stroma-cells grow in wedgewise between cornea primitiva and epithelium.

(*b*) Pupillary membrane: In the anterior vitreous an ectodermal membranous cell-free pupillary-membrane is formed, in mammals this membrane secondarily becomes cellular and vascularised.

(*c*) Anterior chamber: The space between *a* and *b* is first filled up with the anterior vitreous or its substitute; only by its atrophy the (real or virtual) anterior chamber is formed.

3. The endothelium of Descemet's membrane is a mesodermal epithelium.

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OXFORD OPHTHALMOLOGICAL CONGRESS

XVIII ANNUAL MEETING

THE Eighteenth Annual Meeting of the Oxford Ophthalmological Congress was held at Oxford on July 5, 6 and 7 last.

Members met informally at dinner on the 4th in the hall of Keble College, which again offered its hospitality, as in former years. The advantage which is gained by the all too short stay in College, where each member is assigned rooms and becomes for the time being a student, is quite one of the features of this successful annual gathering of ophthalmic surgeons. The proceedings of the Congress were held in the Department of Human Anatomy of the University, kindly lent for the purpose by Professor Arthur Thomson, to whom the Congress owes much. In addition to the Scientific Museum a Commercial Museum was on view, in which fourteen well-known firms of ophthalmic instrument makers exhibited the latest forms of apparatus and instruments.

The proceedings commenced on the morning of Thursday, July 5, with a short address of welcome by the Master, Mr. PHILIP H. ADAMS, Reader in Ophthalmology of the University of Oxford. Immediately following this Professor LEONARD HILL opened a Symposium on the Ultra-Violet Ray, to which the following also contributed:—Mr. W. S. Duke-Elder, Dr. W. J. Turrell, Dr. C. M. B. Dobson, F.R.S., Mr. W. R. Acland, Dr. N. S. Lucas, Mr. G. O. Hume and Mr. A. F. MacCallan; whilst Mr. J. Jameson Evans, Miss Marion Gilchrist and Mr. R. J. Coulter took part in the subsequent discussion.

In his address Professor HILL dealt with the biologically active rays, their measurement and their penetration of the skin and eye, the theory of the action and immunity to rays, the comparison of the sun and lamps as sources, and the action of rays as evidenced by erythema, and touched on haemo-bactericidal power, rickets, ergosterol, vitamin D, and pigment formation.

Some interesting slides of the effect of erythema by ultra-violet ray were shown.

Dr. C. M. B. DOBSON, F.R.S., spoke next on the effect of atmosphere, the altitude of the sun and the presence of ozone on the transmission and the energy of ultra-violet rays. Curves and photographs illustrating these effects were shown.

Dr. W. J. TURRELL gave his clinical experiences of the practical administration of ultra-violet rays, emphasizing the importance of the regulation of dosage. The lamp he favoured was the Tungsten arc lamp which he had used for 13 years.

Mr. W. R. ACLAND dealt with phototherapy in the treatment of dental disease, referring especially to pyorrhoea and its relationship to ocular diseases.

Dr. N. S. LUCAS gave his extremely interesting experiences of the treatment of rickets in Marmoset monkeys by ultra-violet rays, using a mercury vapour lamp. An interesting point observed was the effect upon the eyes when exposed to the rays; a reaction came on much more rapidly, *i.e.*, from one to two hours, than in the human, but passed off more quickly. He considered that some ultra-violet ray dosage was essential to monkeys not in their natural state.

Mr. G. O. HUME spoke on the local application of the rays to the eye in certain conditions, emphasizing the importance of selection of cases and dosage.

Mr. A. F. MACCALLAN, C.B.E., while recognizing the beneficial effect of phototherapy, urged the need for a continued search for causal conditions, notably septic foci in teeth, tonsils, etc.

Owing to illness, Mr. W. S. DUKE-ELDER was unable to be present, and his paper will appear in company with the full report of the Proceedings of the Congress in the Transactions of the Ophthalmological Society of the U.K.

The afternoon was devoted to demonstrations and the examination of ophthalmic apparatus in the scientific and commercial museums.

In the former Mr. E. E. MADDOX showed an Accommodation Balance Test, a new fixation site for the globe in intracapsular cataract extraction and an ingenious apparatus for training amblyopia in squint on a new principle involving hand and eye. Mr. RAYNER BATTEN showed an interesting collection of fundus drawings of diseases and anomalies of retinal and choroidal vessels. Dr. MARGARET DOBSON showed a test for astigmatism in which the duochrome principle was applied to the Maddox "V" Test. Mr. GEORGE YOUNG demonstrated the instruments he now uses in the operation of double sclerectomy for glaucoma which he has devised and also a number of slides in which the effect of the operation could be seen. Mr. W. NICCOL showed slides of a carcinoma of the choroid secondary to carcinoma of the breast, and Mr. B. CRIDLAND exhibited a test-type for children.

At the conclusion of the afternoon's proceedings members and their friends repaired to the gardens of Trinity College for tea, where they were welcomed by Professor and Mrs. R. A. Peters, who kindly acted as host and hostess. The annual dinner of the Congress was held in the evening in the Hall of Keble College and was unusually well attended. Among the guests were the Regius Professor of Medicine Sir E. Farquhar Buzzard, K.C.V.O., Professor Arthur Thomson, Miss Kirkaldy, Dr W. J. Turrell, Dr. C. M. B. Dobson, F.R,S., and Dr. N. S. Lucas. In speaking on behalf of the

Congress, the Master, Mr. PHILIP H. ADAMS, mentioned that 18 new members had been elected during the year, the total membership being now 414, including 8 honorary members. The attendance at the meeting in 1927 was 104, and included a good number of well-known ophthalmic surgeons from the Continent and America. He regretted to have to record the loss, through death, of Professor Felix Lagrange, a Foundation Member, Dr. Brownlow Riddell, Dr. W. J. Tyson, Mr. Fredk. Dale and Mr. T. O'Kelly. The toast of the visitors was proposed by Mr. R. J. Coulter to which Sir E. Farquhar Buzzard replied.

The proceedings on the morning of Friday the 6th opened with a preliminary report by Mr. BURDON COOPER on "Spectroscopy of the crystalline lens," in which he gave, with a lantern demonstration, the results of the spectroscopic examination of normal and cataractous lenses. The spectograms showed that in cataractous lenses potassium was diminished and calcium increased.

Mr. T. HARRISON BUTLER next read a paper on "Sympathetic ophthalmitis" which should be read in the original.

Messrs. S. H. BROWNING, MALCOLM HEPBURN, H. M. TRAQUAIR and A. W. ORMOND joined in the discussion to which Mr. BUTLER replied.

Then followed the Doyne Memorial Lecture, which is undoubtedly the most important contribution to the proceedings of the Congress. Instituted in 1916 in memory of the Founder, the late Robert Walter Doyne, these lectures have proved the occasion for the appearance of much valuable and original work. This year the lecture was by Professor ARTHUR THOMSON, M.A., M.D., F.R.C.S., LL.D., D.C.L., Dr. Lees Professor of Human Anatomy of the University of Oxford, and was no exception to the rule. Prefacing his remarks with a fitting tribute to the Founder, Professor THOMSON chose as his subject "Observations on the Eyes of Birds." After a review of the literature of the past 250 years on the study of the pecten, an exposition of the anatomy of this little understood portion of a bird's eye was given, aided by some excellent slides and models.

It was shown that the most prominent portion of the pecten which projected furthest into the globe was more closely attached to the hyaloid membrane overlying it than it was at its sides. The hyaloid lying upon this black pigmented structure acted as a dark mirror, and the Lecturer suggested that its function might very reasonably be one of elimination of dazzle from direct rays of the sun with reflection of objects from the upper field of vision, to some other part of the retina. The value of this in the case of all birds other than prey-birds would be seen at once. The latter, hovering with its back to the sun in the region of dazzle as far as the ground bird is concerned, is in a position of distinct advantage, whilst the

former, with his enemy in the region of dazzle and thereby difficult to see, is greatly handicapped. If, however, it is true that the bridge of the pecten is a dark mirror, which can eliminate dazzle and reflect the image of the prey-bird, Nature has provided the ground bird with a suitable means of defence. Some excellent photographs imitating these conditions as far as possible were shown, and undoubtedly supported this fascinating and reasonable explanation of the function of the pecten. The subject is one which has received no attention worth notice since the days of Petit, some 200 years ago and Professor Thomson is to be congratulated on his work. The lecture delivered in a very clear and lucid manner commanded the greatest attention and at its conclusion Professor Thomson was presented with the Doyne Memorial Medal for the year.

Mr. G. R. de BEER, Lecturer in Comparative and Experimental Embryology in the University of Oxford, then gave a most interesting paper on some original work which he has carried out on the developement of the vertebrate eye. It would be impossible in a few lines to give the essential points brought out and this valuable contribution to the subject should be read in the original.

On the afternoon of Friday, the Scientific and Commercial Museums were again available but, as an alternative, a visit to the Morris Motor Works had been arranged and the majority of the members availed themselves of the opportunity to see mass production of motor cars.

On Saturday the 7th the session opened with a speculative paper by Lt.-Col. HENRY SMITH, C.I.E., I.M.S. retd., on the nutrition of the lens and vitreous. Comparing the uterus with its rhythmic contractions as a means of maintaining circulation and thereby nutrition, he suggested that a sluice-like action of the ciliary muscle of the eye occurred whereby the canal of Schlemm and neighbouring spaces were opened and relaxed and so aided the circulation of the aqueous humour.

Reports of a series of interesting clinical cases were then given by the following:—

Miss IDA MANN, "A congenital abnormality of the retina." Mr. JOHN ROWAN, "A case of gliomata of the retina" (both eyes removed for gliomata at 1 year and 5 months, no recurrence after over 3½ years). Mr. GEORGE YOUNG, "A case for diagnosis" (enuresis up to the age of 17 which disappeared after correction of some hypermetropic astigmatism). Mr. J. A. ROSS, "Keratitis with intranasal causation" (keratitis of 15 years' standing cured after treatment of an anterior ethmoiditis). Mr. C. G. RUSS WOOD, "Case of Mikulicz's disease with complications." Miss MARION GILCHRIST, "A case of keratitis marginalis profunda occurring in both eyes." All the cases were freely discussed by members. This

concluded the proceedings of as good and pleasant a meeting as has ever been held.

The attendance was well over a hundred, a matter for congratulation as there were practically no members from abroad, owing no doubt to the fact that the International Congress of Ophthalmology will take place at Amsterdam next year.

BRITISH MEDICAL ASSOCIATION
XCVI ANNUAL MEETING, CARDIFF, 1928
Section of Ophthalmology, July 25 and 26

THE PRESIDENT, Mr. F. P. S. CRESSWELL (Cardiff), welcomed the members and called upon Dr. Freeland Fergus (Rothesay) to open the discussion on "Visual Efficiency and Working Ability."

Dr. FERGUS advanced the argument that too much is made nowadays of macular vision or visual acuteness. He entered a plea that much useful manual work can be done by persons who have quite poor macular vision. Uncorrected myopes had little central visual acuity beyond their far point, and he had given details of colliers with high amounts of myopia, who had no difficulty in making as much money as the best-sighted collier could, and what is true of coal-mining is true of almost every other form of manual work. In the peripheral location of objects the sense of projection and the subconscious estimation of distance play an important part. In the former of these the light sense and the colour intensity must be a necessity. In the latter binocular vision and convergence are important, but in the one-eyed individual other factors are of great assistance, namely, the size of the retinal image, the amount of accommodation necessary for fixation, parallax, the size of known objects, etc. The interpretation of retinal images is not a physical process, it is mental. With regard to amblyopia in one eye, the speaker cited a medical practitioner who had no difficulty in driving his motor car, and in carrying on his practice, in spite of this defect. The speaker believed that eyes amblyopic from old convergence had no power of assisting true binocular vision.

Many men who have sufficient sight for their work are thrown out of employment because someone has discovered a trivial defect which has not interfered with the working capacity, but which has caused the insurance companies to refuse the added risk. To some extent the dole is the necessary corollary of the Workmen's Compensation Act. The speaker cited many cases of men doing useful work with very defective sight, and of others who had lost

their employment on account of the detection of an error of refraction.

Sir J. HERBERT PARSONS (London) said that Dr. Fergus had dealt with a relatively small and restricted example of a general principle which was of much wider significance than even he appeared to appreciate. It was a principle which he had tried to elaborate at some length in his book on the Theory of Perception. Every stimulus, tactile, visual or auditory, modifies the complex perceptual pattern upon which it falls, and such a pattern is an integration of all the responses to all the stimuli which the animal is experiencing. Such is not a mere mathematical summation but a psychological integration *sui generis*. One must, therefore, not agree that the signs of visual acuity, 6/6, 6/12, and so on, should be treated as respectable members of the family of fractions, they are not always true to breeding. As a result of a resolution passed by that section at the Portsmouth meeting, the Physiology of Vision Committee of the Medical Research Council had been formed and had carried through a large amount of research work on visual problems.

Mr. N. BISHOP HARMAN referred to the difficulties of the employer in present-day life, who wanted a minimum risk of accident to his employees, and the difficulties of the ophthalmic surgeon who had to do his duty to the employer and the workman in evolving tests of vision. The tests must be made simple of application for the general doctor, easily intelligible by the average man, and yet sufficiently comprehensive to include binocular vision, light and colour sense, accommodation and convergence. The tests must vary with different jobs. Deficiency of one factor must impair the total capacity: all are essential, but their relative importance varies, and all help each other. Fields of vision are needed for work, visual acuity for good work. In school work loss of binocular vision is of little import, but defect of visual acuity for distance or near vision is serious, as it may cause, or be associated with mental dullness or failure of attainment.

AIR VICE-MARSHAL DAVID MUNRO said that after the war a number of officers in the Air Services were examined for permanent commissions. These were men picked out for the services they had rendered in the war, and it was a remarkable fact that out of 178 officers examined 177 had high visual acuity and also good binocular vision. In other words, in the process of self selection the men with lower standards of visual efficiency had dropped out. He thought that for the purpose of flying an aeroplane a high degree of acuity was not necessary, provided that fields of vision were good and that the retinal pictures were correctly superimposed and interpreted by the brain.

Mr. H. CAIGER (Sheffield) was struck with the rapidity with

which men accommodated themselves to monocular vision after the loss of one eye. He knew miners who were earning good wages at the coal face, though they had only 3/60 vision.

Mr. SPENCER (Baghdad) also gave instances of one-eyed individuals, who had been good motor-drivers, pilots of aircraft, and cricketers, before and after the loss of the eye.

Mr. ROBSON (Penarth) had examined several thousand men, and among them were many one-eyed colliers who earned as good wages as the two-eyed men.

Dr. MACKAY (Hull) thought it would be useful to have lists of work which one-eyed men were known to be doing.

Mr. COULTER (Newport) and the PRESIDENT both knew of completely blind men, who were led to the coal face, and earned good wages by hewing coal.

Mr. TUDOR THOMAS (Cardiff) reported that he had noticed in cases of miners' nystagmus that the oscillations were most marked in the eye with the lesser acuity of vision.

Dr. FERGUS replied.

Mr. T. H. WHITTINGTON read a paper on "The examination of the eyes and eyesight of young children." He appealed especially for the examination of children below the school age, and for the examination of children of all classes, not only those attending the school clinics, as was often the case. He suggested certain details of examination in young children, and stated that he preferred test pictures for children of three or four years as a test of visual acuity. He gave standards of vision which might be considered as sufficient at different ages, and gave notes of 4,186 children examined at Queen Mary's Hospital, Carshalton. As a routine, in cases where atropine was necessary, he preferred the use of cocaine and atropine tabloids to ointment. Where symptoms suggestive of eye-strain were present, the possibility of a cure by medical means must always be remembered, in preference to the correction of small errors of refraction.

Mr. FRANK JULER (London) reported a case of bilateral obstruction in the central arteries of the retina, and recorded some observations in unilateral cases which had come under his care.

Mr. R. J. COULTER (Newport) presented some records of his observations on the light sense (as measured by Percival's discs) in 100 cases of miners' nystagmus. His main conclusions were that the light difference and the light minimum were reduced in 41 per cent. of the cases.

Mr. H. CAIGER (Vice-President) was in the chair at the session on July 26, and called on Mr. W. S. Duke-Elder (London) to open the discussion on "The Aetiology of Glaucoma."

Mr. DUKE-ELDER outlined the arguments which made him support the theory that the aqueous humour is formed by a process

of dialysis from the blood plasma, in a way comparable to that taken in the formation of other tissue fluids. He had found by experiment that the aqueous in all conditions is in complete thermo-dynamical equilibrium with the plasma—chemically osmotically, electrically and hydrostatically. With regard to the intra-ocular circulation three factors came into play, firstly an oscillatory flow between the blood and the aqueous depending on the fluctuations of the balancing hydrostatic and osmotic pressures on each side of the capillary walls, secondly, the thermal convection currents in the anterior chamber, and thirdly, a through-and-through pressure circulation from pressure on the outside of the globe by extra-ocular muscles, etc., which caused the aqueous pressure to exceed the venous pressure and the excess to be equalised by escape of aqueous through the canal of Schlemm (a safety valve mechanism.) He next considered how on this theory increase of the intra-ocular pressure might be caused, and classified possible methods as follows:—(1) By altering the equilibrium level: (*a*) by raising the blood pressure in the capillaries; (*b*) by varying the difference between the osmotic pressure of the plasma and the aqueous. (2) Since the sclerotic is practically non-distensible the pressure may also be raised by increasing the volume of the contents of the eye. The only common condition wherein this can occur is when the volume of the vitreous and lens are increased by physico-chemical influences involving changes in turgidity pressure. He dealt with these in some detail and showed how they would explain different types of glaucoma, when the overflow mechanism was interfered with by peripheral synechiae, sclerosis of the pectinate ligament, etc. He concluded, "Taking glaucoma as a pressure symptom merely, I would suggest that the two main factors in its aetiology are these: first, a derangement of the capillary circulation, involving a capillary dilatation which produces a rise in capillary pressure or an increased permeability of the walls, allowing an excess of colloids in the fluids of the eye; secondly, changes of a physico-chemical nature in the vitreous. About the first we know little, but are rapidly learning more; about the second we know less, but are slowly finding out more. . . . Their effect depends directly on the efficiency of the drainage channels in the region of the angle of the iris."

Mr. THOMSON HENDERSON (Nottingham) said that he was unable to accept the theory put forward by the opener of the discussion. The eye, like the cranium, is a closed unyielding capsule with a total fixed volume. In such a system, the intra-ocular fluid contents lie and vary with the pressure in the exit veins, because this pressure is the lowest circulatory pressure within closed spheres of eye and brain. With the ophthalmoscope, it can be seen how the slightest pressure on the globe causes constriction at the

exit of the retinal veins. If the cerebro-spinal fluid and the aqueous were formed by dialysis, the dialysing membrane being the walls of the capillaries, there would be no necessity for such special and highly vascular structures as the choroid plexus and the ciliary processes. The great variations in the severity of the clinical manifestations of glaucoma point to the existence of two primary influences in its production. The first is a constant and predisposing factor, a pathological excess of the physiological sclerosis of the cribriform ligament, whereby the contact of aqueous with Schlemm's canal is diminished. The second factor is variable, exacting and vascular in origin : as the contact of aqueous with veins is reduced, the intra-ocular fluids act as a rigid volume, which operating through the tissues, converts the intra-ocular circulation from an elastic to a rigid system of tubes, in which the venous pressure is raised,and with it *pari passu* the intra-ocular.

Mr. BISHOP HARMAN (London) said that the eye was the scene of a fight between the anatomists and the physiologists. The possibility of medical treatment for glaucoma was attractive, but the fear of delay and non-success drew him to surgery. There was no doubt of the various anatomical defects in the glaucomatous eye, and of the usual success of measures devised to help the excretory channels. In the present state of our knowledge, his clinical experience led him to stress the anatomical factors as of the first importance in the disease.

Mr. A. W. ORMOND (London) had found the new conception of the causes of glaucoma useful in his own comprehension of the disease. Dale, by his intravenous injection of the chemical toxin, histamine, had produced rise of tension, and possibly also it might be produced by a bacterial toxin. All the signs of inflammatory glaucoma might be explained by a capillary dilatation, but he believed that there were many types of glaucoma, each with a varying cause. He expressed some doubt as to whether the more chronic types were due to alterations in the intra-ocular capillary pressure. He was sure that Priestley Smith's predisposing causes still held.

Dr. R. H. PARAMORE (Rugby) threw doubt on the dialysis theory. If the hydrostatic pressure within the capillaries was greater than that of the tissue fluids outside those capillaries, the latter would dilate until equilibrium was obtained, or they would burst. He doubted if the reputed difference in respect of permeability of capillary walls in different parts of the body, as shown for instance by variations in the composition of lymph, was not due rather to a difference in the nature of the related tissue cells than to specific differences in the walls of the capillaries. With regard to histamine, it was essentially a tissue cell poison, and he thought that the results were to be explained by its effect on the

tissue cells rather than on the capillaries. From what Mr. Duke-Elder had said with regard to the vitreous, it appeared to him that the swelling of that gel was a more likely cause of the increased tension. Neither a dilatation nor an increased permeability of the capillaries seemed necessary.

Lieut.-Col. A. E. J. LISTER (Bristol) said that anatomical factors must play a part, for microphthalmic eyes were liable to the disease, and he had seen it in a young patient with a small coloboma of the iris. He also cited a case where the attacks were definitely brought on by sewing for a few hours, the tension being quite normal as measured by the tonometer in the intervals. This suggested a convergence factor, with pressure from the exterior. In reply to a suggestion by Dr. SPENCER (Baghdad), he had not seen in India any suggestion of a connection between trachoma and glaucoma.

Messrs. CYRIL WALKER (Bristol), HARTY (New Zealand), QUICK (Swansea), and PRIMROSE (Glasgow) also spoke, and Mr. DUKE-ELDER replied.

Mr. A. H. LEVY (London) read a paper on "Telescopic Spectacles."

Mr. BISHOP HARMAN demonstrated an instrument (made by Weiss) designed to assist in the mapping out of central scotoma of the visual field.

ABSTRACTS

I.—MISCELLANEOUS

(1) **Finoff, William C. (Denver, Colorado).—Dry sterilization for eye instruments.** *Amer. Jl. of Ophthal.*, August, 1927.

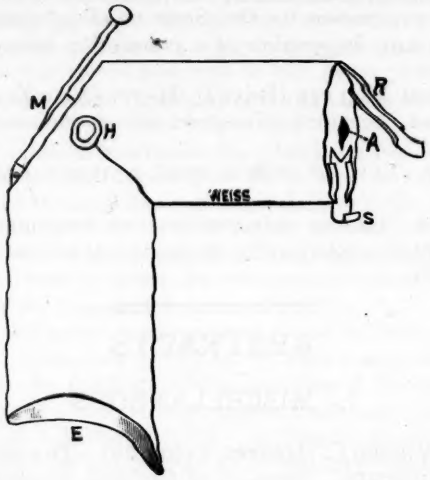
(1) **Finoff** was led to use this method by the work of Morax, who had found it the most satisfactory way of sterilizing ophthalmic instruments. The knives remain polished, the points being uninjured and the edges sharp. The method is as follows: Knives are fixed in holders and placed in corked test tubes. Other instruments are arranged in metal boxes with tight fitting covers. Each container is wrapped in two layers of paper, labelled and placed in an electric sterilizer which keeps the temperature at 320° F. for a period of half an hour. At the time of operation the paper is removed and the sterile containers handed to the surgeon, who can open them as he desires. Once sterilized the instruments can be kept indefinitely and the only objection to the method is the necessity of having more than one set of instruments, if a second operation of a similar character is done the same day.

F. A. WILLIAMSON-NOBLE.

(2) **Bishop Harman, N.—The scotograph: an instrument designed to facilitate the fields of vision where there is a central scotoma.** (*Abstract of paper read at The Ophthalmological Society of the United Kingdom.* April, 1928.)

(2) Field taking is difficult where the macula of one eye is out of action. The device shown gets over most of these difficulties.

A tube is bent at a right-angle midway in its length, and the two arms are so arranged as to give the seeing eye a false fixation spot which will correspond in position to the real one marked on the perimeter or scotometer.



The figure shows the plan of the instrument in reduced scale. E is the eyepiece. At the knuckle there is a double circle marked H, for the reception of the handle. At the extreme right-hand end of the tube is a plate, in the centre of which is cut a diamond-shaped aperture. At the knuckle of the bend of the tube is a large hole covered with a hinged lid, M, fitted inside with a plane mirror.

The patient holds the instrument before the eye which has fixation power. He sees the patch of light reflected from the mirror lid at the knuckle. The field of vision of the other eye and the scotomata are thereon mapped out. The instrument can be used for either eye.

The scotograph is made by Messrs. Weiss. It has been shown with the handle for holding in the hand of the patient, and this is the form I prefer, but the makers are prepared to fit it with a crank arm to clip on the upright of the perimeter.

BOOK NOTICES

Der graue Altersstar, seine Ursachen und seine nichtoperative Behandlung. By Dr. A. SIEGRIST, Director of the University Eye Clinic, Berne. Pp. 399. Berlin and Vienna, 1928.

The greater part of this monograph is devoted to a critical discussion of the theories of causation of senile cataract. Thirty-seven pages suffice for the history up to 1877, when a new era opens with the work of O. Becker. Becker's theory of malnutrition associated with irregular sclerosis of the lens, regards cataract as an almost physiological phenomenon, whereas Deutschmann on similar grounds regards it as entirely pathological. Schön attributes cataract to abnormal strain of accommodation, Magnus to malnutrition. More worthy of credence are the theories of Hess and Römer. The former regards the deleterious effect of toxic influences upon the capsular epithelium as the essential feature, but gives no definite evidence of the nature of the toxins. Römer's theory is founded upon the facts and fantasies of immunology, wherein cytotoxins play the chief rôle. Both theories have been severely criticized by Vogt. The fact of the frequent association of cataract with tetany which is now known to be due to parathyroid insufficiency and disordered calcium metabolism, led Peters to elaborate a theory which probably embodies a very important element in the aetiology. Siegrist discusses the tetany theory at length including the very striking experimental results obtained on animals by Possek, Edmunds, and others, as well as by Hiroishi, performed under his supervision.

These observations, the association of cataract with dystrophia myotonica (myotonia atrophica), and many other indications, have led Siegrist to the conviction that cataract is a result of disturbance of the endocrine glands. There is much to be said in favour of this hypothesis, and it is all well set out, with ample bibliography, in this work. For this reason the book is a welcome addition to the ophthalmologist's library.

The portions dealing with the non-operative treatment of cataract show how easily a scientific outlook may give place to extravagant empiricism in the same individual. They are of some interest as an enumeration of the various applications which have been tried and in the opinion of most competent ophthalmologists been found wanting. The crude endocrine mixture used by Siegrist does not, on his own showing, appear to have given any very definite results, and the name which he has applied to it—euphakin—will hardly commend it to English surgeons.

The Prescribing of Spectacles. By A. S. PERCIVAL, M.A., M.B., B.C.Camb. 3rd edition. Rewritten. Pp. 236. Bristol: John Wright and Sons, Ltd. London: Simpkin Marshall, Ltd. 1928. Price 15s. net.

Percival, in the third edition of his well-known book, carries out the injunction often given to a post-prandial speaker, that he should dig deeply into his subject, but not bore. A book on the prescribing of spectacles might conceivably be one of the dullest imaginable, but the particular one under review is the very reverse, because it contains such a wealth of interesting, and often original observations. Thus, to quote only two :—If the ametrope hold a pinhole diaphragm 3 inches in front of the eye, and move it slightly up or down, his attention being directed to the distant test types, the latter will appear to move. If the vertical meridian of the eye be myopic, the apparent movement is the same as the movement of the diaphragm, if hypermetropic it is in the opposite direction. Again, in testing for eso- or exophoria with the Maddox rod: if the red line appears to be continually shifting its position anisometropia or paresis is probably present. Even so small an error as 0.25 D is often revealed by this method, and when the necessary addition is made to one or the other eye, the line remains stationary.

The author's work on the effectivity of cylinders in reading glasses is probably known to many readers of this Journal. It is fully described in his book, and its mathematical basis is also given. The work would seem to be important, since in some cases the difference between the effective power of a cylinder when used for distance or for reading may amount to as much as 9 per cent., also the axes may require alteration, as when the eyes are converged and depressed there is often some extorsion. The section on heterophoria and the use of prisms contains much that is of interest and value. It is more than likely that many cases of obstinate asthenopia, where symptoms persist in spite of adequate correction of errors of refraction, could be cured by the prescription of prisms on the somewhat original lines laid down by the author. The book concludes with a section on Optics, in which the question of periscopic lenses is dealt with at some length. It is characteristic of the author that he should point out that what is needed is not a lens which will give good definition in the peripheral part of the field when the eye is looking through the centre of it, but one which will allow for the range of rotation of the eye behind it, and allow the fovea to see clearly through any part of the lens when directed towards it. The conditions are therefore quite different from those governing the design of a photographic lens in which the camera stop is fixed, and does not move about in the way the iris does.

Enough has been said to show the general character of this book.

When reading it, one feels that it is the work of a master who does not mind departing from some of the ordinarily accepted conventions when his reasoning seems to indicate the necessity of doing so. The book is therefore very stimulating to read, and brings much new light to bear on many of the problems of refraction.

Die epidemische Mangelhemeralopie (sog. Essentielle Hemeralopie). Eine Beitrag zur Lehre von den Avitaminosen. By Dr. Th. BIRNBACHER, Vienna. Berlin: S. Karger. 1927. Pp. 62, with 8 text illustrations. (Special edition of part iv. of the Treatise on Eye Disease, edited by Prof. J. Meller.)

This monograph by Birnbacher deals with observations on the epidemic of night-blindness with xerosis which occurred in Vienna in the years 1919-1924. The highest point was reached each year in May. The number of cases dealt with was 330, of which 292 were males and 38 females. In all the cases in which night-blindness was complained of light sense, as measured by the Birch-Hirschfeld apparatus, was diminished. The fundus showed no change in practically all the cases and oedema of the papilla or retina was never observed. Treatment with liver was followed by a rapid cure, but relapses occurred in 27 per cent. of the author's own cases. In all the cases foods containing vitamine A (milk, butter, eggs, fat) were deficient in quantity. Xerosis occurred most frequently in the younger patients, in whom also other signs of malnutrition were more evident. Kerato-malacia corresponded in its period of maximum intensity with night-blindness, *i.e.*, May of each year. Birnbacher suggests that the great preponderance of males affected as compared with females bears a relation to the development of sperm cells which require a large vitamine content. He concludes by pointing out the necessity of a clear differentiation between the so-called essential or idiopathic night-blindness here described, which belongs to the dystrophia xerophthalmica of Blegvad, and other forms of night-blindness due to disease, and suggests that this disease might be termed deficiency-hemeralopia (*Mangelhemeralopie*).

A bibliography containing 93 references adds considerably to the value of this little work.

NOTES

Appointments

MISS IDA MANN has been appointed Ophthalmic Surgeon to the Royal Free Hospital.

MR. F. RIDLEY has been appointed Pathologist to the Central London Ophthalmic Hospital.

Honour

THE KING has been pleased to confer the honour of C.B.E. on Mr. D. R. Wilson. Our readers will be familiar with his work as Secretary of the Physiology of Vision Committee, Medical Research Council, and of the Industrial Fatigue Research Board. He was President of the Illuminating Engineering Society last year.

* * * * *

The Illuminating Engineering Society

THE death of Mr. Leon Gaster has rendered it advisable to make some alterations in the constitution of this Society. Mr. D. R. Wilson, the President, has sent a circular letter on behalf of the Council to the members stating that an entirely revised constitution is in course of preparation, which will, if adopted, cause the government and the administration of the Society to be much more like that of other Societies than has been the case under the old constitution. Further, that, while the Society is in a sound condition as far as its present rather restricted scale of activity goes, attempts are being made to secure a much wider support. All interested in the hygienic aspect of good lighting will hope that these efforts may meet with success.

CONTEMPORARY OPHTHALMIC LITERATURE

American Journal of Ophthalmology. *July, 1928.*

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CLAPP, C. A. Preliminary report upon experimental investigation as to presence of treponema pallidum in luetic interstitial keratitis.
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BANISTER, JOHN M. Surgical suggestions as to individual paralysis of the oblique ocular muscles.
MUSKAT, IRVING I. Milk injections in gonorrheal ophthalmia.
SPARE, A. Tapetoretinal degeneration of the retina.
KNORR, ERNEST A. One hundred senile cataract operations at the Presbyterian Eye, Ear, Nose, and Throat Hospital, Baltimore.

Archives of Ophthalmology. *July, 1928.*

KIRBY, DANIEL B. A modified Motais operation for blepharoptosis.
LANCASTER, WALTER B. The Ames spectacle device for the treatment of cyclophoria, with a report of a successful case.
MARLOW, F. W. Eye-strain in relation to functional neurosis.
ADLER, FRANCIS HEED. A comparative study of the rôle of pigment in the physiology of vision.
TASSMAN, I. S. The proteins of the lens and their chemical changes in the pathogenesis of senile cataract.
WOOTTON, HERBERT WRIGHT. A case of glioma of the optic nerve.
CASSELL, JAMES WILSON. Some observations of the eye clinic of Dr. Henry T. Holland, at Shikarpur, India.
AGATSTON, S. A. Fundus as a definite index to arterial disease, with analysis of 100 cases.

WEXLER, DAVID. Ocular depigmentation accompanying generalized vitiligo. Report of a case.
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